



Journal of the  
American Osteopathic College  
of Dermatology

# Journal of the American Osteopathic College of Dermatology

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AOCD  
1501 E Illinois Kirksville, MO 63501  
800-449-2623 FAX: 660-627-2623  
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# Letter From The JAOCD Editors



**Jay S. Gottlieb, D.O.**



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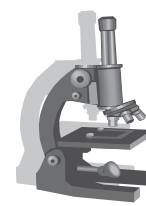
**James Q. DelRosso, D.O.**

As editors of the JAOCD it gives us great pride to say that this is our second issue of the JAOCD. From the feedback that we have received, the first issue was met with a warm welcome and was considered a success by all. We want to thank the contributing authors and our inaugural corporate sponsors who have helped launch both the inaugural issue as well as this current issue. We anticipate that all our readers will enjoy this second issue of the JAOCD.

The mission of the Journal of the American Osteopathic College of Dermatology remains to better serve the continuing educational needs of the AOCD members, residents and the dermatology community at large. The JAOCD will remain a vehicle for our residents to have the opportunity for their required papers to be published during their residency program.

We will continue to include the following areas in the JAOCD: Dermatologic therapeutic modalities; Original presentation of research; Brief opinions; Clinical studies; Case reports; Basic science as it relates to dermatology; Cutaneous surgery; Dermatopathology; Cosmetic dermatology; Pharmaceutical dermatology; Editorials; Letters to the editors; Pearls and anecdotes in dermatology.

Again, we extend our sincere appreciation to our Founding Sponsors: Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services, Novartis Pharmaceuticals Corporation, Medicis-The Dermatology Company and 3M Pharmaceuticals. Without their continued support we would not be able to have a journal to serve the AOCD.



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Jay S. Gottlieb, D.O., F.O.C.O.O. (Editor)  
Stanley E. Skopit, D.O., F.A.O.C.D. (Editor)  
James Q. Del Rosso, D.O., F.A.O.C.D. (Associate Editor)



Stanley Skopit, D.O., F.A.O.C.D.  
President

We have come along way since the inception of our college in 1957 when the American Osteopathic College of Dermatology was recognized as a separate specialty within the American Osteopathic Association. There are now over 300 members, 16 residency programs throughout the United States, training 62 residents. The AOCD is the organization responsible for residencies and Continuing Medical Education nationwide.

The college organizes two national CME programs yearly. This year the annual meeting & scientific seminar of the AOCD took place October 2003 at the AOA convention in New Orleans and the midyear program is scheduled for April 2004 in Tucson, Arizona under the Program Chair of Bill Way, D.O. at the host hotel, Hilton Tucson El Conquistador.

As President of the AOCD over the next year, my goals & objectives will revolve around the current AOCD five year plan which serves as the College's mission statement:

1) Education & Awareness Programs lead to higher quality residency programs, CME programs & Public Awareness Programs through the public service awareness poster campaign; 2) Increasing membership opportunities for current & future meetings in order to maintain unity with "strength in numbers" within the AOCD; 3) Dealing with challenges that face our college & profession of Dermatology with regard to changes in our medical practice in the 21st century; 4) Diplomacy through efforts to gain the American Academy of Dermatology as our ally in economic unity; 5) Maintaining & securing corporate membership relations to help support our College financially; 6) Updating & maintaining the Administrative Policy Manual; 7) Establishing the AOCD foundation; 8) Pursuing of Fellowship by AOCD members are encouraged; and 9) Promoting the Journal, JAOCD.

Stanley Skopit, D.O., F.A.O.C.D.

# Osteopathic Medicine and Dermatology

## The role of the D.O. in the prevention and treatment of skin disease

by Robert A. Norman, D.O., MPH

The role of osteopathy and osteopathic treatments in dermatology has received little attention. I will focus on a few key areas and will provide the results of my experience with using osteopathic techniques to improve care and save costs for my patients. Osteopathic techniques in the general osteopathic exam, including the skin exam, and diagnosis, prevention, and treatment of wounds will be reviewed. By carefully studying and implementing these findings, the practicing clinician can not only save his or her patients much discomfort and costs but also adhere to the practice and principles which form the basis of osteopathic medicine.

It is unfortunate when the pace and pressures of modern medicine discourages the practicing osteopathic specialist to incorporate the wonderful techniques of osteopathy in his or her practice. Within dermatology, for example, it is possible to simply prescribe one medication after another (dermatologists write more prescriptions than any other practitioner) without looking into the skin signs of systemic disease or the powerful inherent tools we have to heal naturally. The techniques originally put in motion by Dr. Andrew Taylor Still can consistently inform the lives of all practitioners, no matter how much one specializes.

Many of the basic skills of the osteopathic exam can truly shine in the dermatological evaluation. Why is a patient's psoriasis so flared at this point in time? Why now? Is there a particular stress going on in the patient's life? All of these questions and more are essential for the good dermatological history.

### General Dermatology

The skin houses an enormous variety of roadmarks for systemic disease. The first clue of HIV infection is often the emergence of a skin disease. If the practitioner pays attention to the skin, early diagnosis and aggressive therapy are possible.<sup>(1)</sup>

I have noted underlying osteopathic dysfunction in many patients complaining

of dermatological manifestations.

The definition of tissue texture abnormality (TTA) includes many of the signs found in skin abnormalities, including vasodilation, edema, fibrosis and the symptoms of itching, pain, tenderness, and paresthesias<sup>(2)</sup>. Types of TTA include thickening, stringiness, ropiness, firmness, and changes in temperature and moisture. When examining the lower extremities of patient, for example, many of the signs and symptoms taught in osteopathy become apparent. A patient with stasis dermatitis may complain of itch and examination may reveal color changes, fibrosis, xerosis, increased temperature, and other symptoms of compromised circulation. Prime considerations are improving blood flow including using osteopathic techniques.

As Kelso et al have shown in their thermographic measurement research, warm skin areas of somatic dysfunction can be changed by OMT<sup>(3)</sup>. Adams et al explored the regional differences in palpatory characteristics of the skin when exploring abnormalities of tissue texture<sup>(4)</sup>.

In 1938, SE Stanley wrote the article "General considerations of cutaneous therapeutics: underlying causes should be studied to insure greater success in treating skin conditions" in the journal *The Osteopathic Profession*. In the article, Dr. Stanley points out that physicians tend to neglect seeking an etiology for skin diseases and skin manifestations and that correct diagnosis involves not only naming the disease but also seeking the etiology and developing a treatment plan on its basis. Dr. Stanley stated that osteopathic manipulation is the most valuable treatment mode because it deals directly with the circulation and nervous system which is involved with skin disorders<sup>(5)</sup>. Dr. AE Scardino noted in the article "Dermatology: discussion of common lesions: chemophysical therapy and manipulation efficacious for refractory skin diseases" in the April 1942 *The Osteopathic Profession* that osteopathic manipulation is recommended for skin diseases since it deals with motor and sensory nerve supply and trophism<sup>(6)</sup>.

Stasis dermatitis occurs with venous insufficiency, pedal edema, and varicose veins. The brownish color results from hemosiderin deposition. The disease can lead to increased susceptibility to ulceration or cellulitis. Acute exacerbation of stasis dermatitis can result in "id" reaction or autosenesitization dermatitis, producing secondary, acute, papulovesicular, often symmetrical distribution on the extremities.

Chronic venous insufficiency is due to venous hypertension secondary to valvular incompetence. Factors include hereditary, prolonged standing, venous thrombosis and may manifest as edema, varicosities, brown discoloration, superficial neovascularization, dermatitis, and venous ulcers. Therapy includes elevating the legs, exercise, supportive stockings, surgery, mild to moderate corticosteroids and oral antibiotics if secondary infection is present.

Stasis dermatitis and chronic venous insufficiency are two common dermatological conditions which can be improved with osteopathic evaluation and treatment. In a similar fashion to primary care, the task of the dermatologist and others who treat dermatological disease is often filled with treating the external manifestations of stress. Almost all skin disease appears to flare during exacerbations of stress. Therefore, techniques acquired during osteopathic training of stress reduction, including OMT, and in many institutions acupuncture, meditation, and other modalities, all can be used to treat our patients.

A holistic approach is crucial to achieving comprehensive results. A skin specialist can remove a skin cancer, but would not be doing a complete job if he or she ignored the overall behavior that provokes unhealthy skin. Smoking cessation education in appropriate patients, for example, is an integral part of patient care for all practitioners. We are finding more and more evidence that smoking increases the incidence of skin cancers, ulcers, and other skin abnormalities.

Education has always been a key component in the osteopathic physicians' armamentarium. Sun protection, such as using sun block and wearing protective clothing, along with avoiding high intensity mid-day sun is crucial for our patients' wellness.

## Wound Care

### Overview

A pressure ulcer is a localized area of trauma resulting from lack of blood supply to the involved tissues. Although many factors contribute to the development of pressure ulcers, the four most critical are pressure, shearing forces, friction, and moisture. Pressure results in ischemia and tissue damage. Shearing forces occur when layers of tissue slide on each other and twisting and stretching of blood vessels results in subsequent ischemia and damage. Friction is the force created when two surfaces in contact move across each other, such as when a patient is pulled across the bed sheets, thus eliminating the outer protective stratum corneum and accelerating the ulcerative process. Moisture from urine, feces, wound exudate, or perspiration leads to skin maceration and increased risk of ulceration.

The vast majority of pressure ulcers occur on bony prominences in the lower part of the body, with the sacral and coccygeal areas, ischial tuberosities, and greater trochanters accounting for the majority of sites. Other frequently involved areas include the fibular head, malleolus, heel, and the medial condyle of the tibia.

The consequences of pressure ulcers are multiple and life-threatening. Ulcers can be a source of sepsis and osteomyelitis, pyarthrosis, joint disarticulation, and systemic amyloidosis.

### Chronic vs. Acute wounds

A chronic wound is defined as a loss in tissue integrity produced by insult or injury that is of extended duration or frequent recurrence. An acute wound is one in which simple medical or surgical intervention produces a resolution.

In homo sapiens, wound healing occurs by repair vs. regeneration. Only hepatic and epithelial tissues are capable of regeneration in man. In the toad, obliteration of a limb can result in regenerating a new one identical to the original. In man, wounding that injures the dermis signals the body to restore the structural integrity via the synthesis of new tissue different than the originally present. The type of wound and mechanism by which the wound is closed depends on the extent of

injury and the type of tissue injured. In chronic wounds, the healing time is longer and can be phased using markers such as the Clark model. Clark categorized healing into three phases--inflammation (from the moment of injury to approximately four to six days post injury), granulation tissue production (day 4 to 21 and matrix formation and remodeling (3 weeks up to 2 years). Key cells in phase one include platelets, neutrophils, lymphocytes, and epithelial cells. Macrophages play a crucial role in all three phases. Fibroblasts are important in phase 2 and 3.

With superficial wounds, where only the epidermis or dermis is injured (partial thickness wound) may heal rapidly via the process of re-epithelialization. Epithelial cells migrate toward one another from the edges of the wound, from the hair follicles, sebaceous glands, and sweat glands and eventually close the wound.

### Wound Recurrence factors

Chronic wounds often result from surgical procedures, traumatic insults, or metabolic, infectious, or neoplastic disorders. Pressure ulcers, diabetic ulcers, lower leg ulcers, vascular ulcers, post-operative open wounds, and enterocutaneous fistulae are frequently occurring chronic wounds. Non-healing wounds generally occur in older individuals with multi-system problems, poor medical care, and inadequate health habits. Chronic wounds often arise as a result of diabetes, cancer, liver, renal, or gastrointestinal illness. Radiation trauma victims, transplant patients, and burn patients often suffer with chronic wounds. Drug therapy such as steroids can make a person more prone to wound development. Obesity, smoking, poor nutrition, and immobility can delay wound repair.

Given the many factors that predispose our patients to chronic wound development, it is obviously crucial for any physician or caregiver to carefully assess their patients and work on preventive strategies such as weight control, smoking cessation, proper nutrition, and appropriate drug usage. Wounds represent an enormous burden to our patients' economic and psychological well-being. The prevalence of chronic non-healing wounds can only be estimated. In 1989 in the United States, approximately 2,100,000 people had pressure ulcers, 3,000,000 had diabetic ulcers, 500,000 had vascular ulcers, 6500 had open wounds or fistulae, for a total of 5,606,500. The cost to heal a single pressure ulcer can range between \$400 and \$40,000<sup>(7,8)</sup>.

As an osteopathic practitioner, we can help in cost-saving efforts by practicing

good osteopathic skills in wound care. Evaluating areas of skin congestion with our palpatory skills can signal the clinician to write orders to make sure the patient is turned off the congestion area, thus preventing further pressure and ulcers.

As part of my clinical investigation when writing this article, I examined twenty patients with previous documented ulcers for signs of osteopathic lesions, particularly in the sacroiliac and lumbar areas. Of these twenty patients, twelve had areas consistent with stage one ulcer formation.

By using osteopathic palpatory skills, I was able to document pre-ulcer conditions and review preventive findings with the nurses on duty. Included were recommendations on proper nutrition, ambulation when possible, and circulation enhancing suggestions. In follow-ups six and 12 months later, the results were dramatic. Although one of the patients succumbed to conditions unrelated to his previous wound problems, none of the remaining 11 patients had developed further ulcer formation. Two of the remaining patients had stage two ulcer formation, and with osteopathic evaluation were reduced to stage one, and eventually also cleared up. In addition, the nurse commented that the introduction of palpatory skills into their caretaking regimen helped improve the condition of all their patients.

In summary, osteopathy and osteopathic treatments play a crucial role in dermatology. I hope this article triggers other specialists to examine the fundamental importance of osteopathic principles in helping their patients achieve maximum benefits.

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# Disorders of Cornification: The Multiplex Presentation of Ichthyosis

Angela L. Phipps, D.O., B.S.N., R.N.

## Abstract

*The term ichthyosis is derived from the Greek word ichthys meaning fish.<sup>1</sup> The ichthyoses are a heterogeneous group of diseases that share one presentation: scaly skin. The outermost layer of the skin that is contiguous with the environment is the epidermis. The cell kinetics of the epidermis are altered with the ichthyosiform disorders and results in the clinical appearance of skin that resembles the scales of a fish. The keratinocyte is the principle cell of the epidermis.<sup>2</sup> The ichthyoses represent abnormalities in the formation and desquamation of these keratinocytes. The keratinocyte has a specialized function to produce filamentous proteins called keratins that form the structural framework inside the cell. To understand the ichthyoses, one must be familiar with the internal to external progression of normal skin.<sup>3</sup> In this progression, the keratinocytes progress through the epidermal layers (stratum basalis, stratum spinosum, stratum granulosum, stratum corneum) manufacturing proteins in a predictable sequence. Errors in this manufacturing process will result in mutations that alter the skin's physical appearance and function.*

## Ichthyosis Vulgaris

### Description and Epidemiology:

Ichthyosis Vulgaris (IV) is a disorder of cornification that presents with a very fine, "collaret" scale that appears "pasted-on" over the entire cutaneous surface. It has an autosomal dominant inheritance pattern and is characterized by onset in early childhood, usually between 3 and 12 months of age.<sup>4,5,6</sup>

This common condition occurs in approximately 1:250 to 1:500 persons.<sup>3,4</sup>

### Pathogenesis:

IV is a retention hyperkeratosis with normal epidermal proliferation. The keratinocytes are unstable due to the defect in the keratohyaline granule's major protein- profilaggrin.<sup>3</sup> Standard skin biopsies stained with hematoxylin and eosin of patients with IV show a granular layer that is diminished to absent.<sup>2,3,7</sup> The keratohyalin granules appear spongy or fragmented on electron microscope (EM).<sup>5,6</sup>

This correlates with reduced profilaggrin expression. Filaggrin is not detectable in the involved epidermis.<sup>5,8</sup> No gene defect for reduced profilaggrin has been found to date.<sup>2</sup>

### Clinical Aspects:

Children with full-blown IV have fine white scales from the neck to the ankles, sparing the axillary and gluteal folds (where humidity is higher). The face is also usually spared (where the sebaceous glands help to control scaling).<sup>3</sup> The extensor surfaces of the extremities are most prominently involved.<sup>4,5</sup> Varying degrees of dryness of the skin may be evident. The scales are coarser on the

lower extremities having a lizard-like appearance. Finer scales are seen on the trunk that resembles small bran flakes. The palms often are dry and show hyperkeratosis and accentuated skin markings referred to as "hyperlinear palms."<sup>3,5</sup> Keratotic lesions (keratosis punctata) may be found on the palmar creases.<sup>9</sup> The scalp is involved with only slight scaling.<sup>5</sup>

The hair, teeth, and nails are normal.<sup>3</sup> IV is frequently seen in association with atopic dermatitis and keratosis pilaris. Although the antecubital and popliteal fossae are usually spared by IV, atopic changes may be present. Atopy manifested as hay fever, eczema, asthma, or urticaria is frequently present.<sup>2,5</sup>

### Laboratory:

A skin biopsy from a patient with IV will display an absent granular layer. The EM finding of abnormal keratohyalin granules is the gold standard in making the diagnosis.<sup>6</sup>

### Prognosis:

The course of IV is favorable. It usually improves in the summer and in warm, moist environments. It tends to improve with age and has limited findings by the time the patient is an adult.<sup>6</sup>

### Therapy/Management:

IV can be controlled but not cured. The initial step is to hydrate the stratum corneum and seal in the moisture. Simple soaking in warm water followed quickly by application of a thick, greasy moisturizing cream or ointment is sufficient for most patients. Soaking twice daily is preferable, as long as sufficient moisturizing cream or ointment is applied immediately after the bath.

Moisturizers that are available in jars and scooped out with the fingers work best. This includes petroleum jelly and even vegetable shortening. More elegant solutions include mild keratolytic agents (salicylic acid), alpha hydroxyl acids or propylene glycol.<sup>3</sup> Keratolytics help loosen the upper layer of scales and promote shedding. Alpha hydroxy acids (lactic, citric, and glycolic) are simple, organic, hygroscopic acids that both hydrate the skin and cause the skin cells to detach. It is important to note that alpha hydroxy acids sting and that most children do not tolerate them. When applied to the entire cutaneous surface, any acid preparation can cause acidosis in neonates and, therefore, should not be used.<sup>3</sup>

## X-linked Ichthyosis

### Description and Epidemiology:

X-linked Ichthyosis (XLI) is another disorder of cornification that can clinically be difficult to distinguish from IV depending on the severity. However, XLI typically presents with a larger, coarser, dirty appearing, brown scale. It is more prominent on the anterior neck, extensor surfaces of the extremities, and the trunk. This is an uncommon form of ichthyosis that occurs only in males.<sup>3-6</sup> The incidence ranges from 1:2000 to 1:6000 births with onset usually before 3 months of age.<sup>2,3,6</sup> The mother is an obligate heterozygote. Spontaneous parturition has often failed to occur when these patients were born, owing to a placental sulfatase deficiency.<sup>5,10</sup>

### Pathogenesis:

XLI is due to a deletion error of the X

chromosome at Xp22.<sup>3,2-6, 11, 12</sup> This deletion results in a deficiency of the enzyme steroid sulfatase in the patient's fibroblasts, leukocytes, and keratinocytes. Without the presence of the enzyme steroid sulfatase, cholesterol sulfate accumulates causing the abnormal cornification.<sup>5</sup>

### *Clinical Aspects:*

In patients with XLI, desquamation of the skin is seen within a few weeks or months after birth.

Dark brown scaling of the extensor surfaces of the arms and legs, trunk, and especially the sides of the neck are observed. The scales are tightly adherent to the skin. The parents will report an unwashed look to the child's skin and will often vigorously scrub these regions to try and remove the "dirt." The elbow and knee flexures are relatively spared, as are the central face and scalp.

Scaling can be seen around the ears and lateral cheeks. The palms and soles are nearly always spared. Hair, nails, teeth, and mucous mucosa are not affected. The classic areas of involvement are the lower abdomen and sides of the neck. Marked seasonal variation is seen and warm weather ameliorates the scale. Placental sulfatase is needed for labor to progress. Some mother's report prolonged labor or failure to initiate labor when carrying children afflicted with XLI.<sup>2-6, 10</sup>

In contrast to IV, keratosis pilaris is not seen and the incidence of atopy is not abnormally high.<sup>5</sup>

Punctate corneal opacities and cryptorchidism are the hallmark extra cutaneous manifestations associated with XLI. Slit lamp examination will reveal punctate corneal opacities on the posterior capsule or Descemet's membrane in approximately 50% of affected males and female carrier mothers.<sup>13, 14</sup> Cryptorchidism is noted with a 12-15% incidence and an independently increased risk of testicular cancer.<sup>5, 15, 16</sup> Patients affected by XLI also have a reduction of sweat glands and a decrease in sweat production.<sup>17</sup>

### *Laboratory:*

With XLI, the clinical differentiation from Ichthyosis Vulgaris (IV) at times may be difficult. The diagnosis of XLI can be made or confirmed by lipoprotein electrophoresis. The increase in cholesterol sulfate makes the LDL migrate much more rapidly. However, this test is difficult to obtain.<sup>5</sup> The decrease in steroid sulfatase can be measured by three methods: (1) enzyme assays, (2) cholesterol sulfate

accumulation in various tissues, and (3) fluorescent in situ hybridization (FISH) test.<sup>3</sup> The reduced enzyme activity can be assessed in fibroblasts, keratinocytes, leukocytes, and prenatally in amniocytes.<sup>5</sup> If the gene deletion is known, the FISH test is useful for prenatal diagnosis.<sup>3, 18</sup> The blood test for excess cholesterol sulfate is the most reliable method for affected males.<sup>2</sup>

### *Prognosis:*

X-linked ichthyosis is a lifelong condition that does not improve with age. Unlike IV, it can gradually worsen in both extent and severity. However, it is not debilitating and should not adversely affect normal life activities.<sup>3, 5</sup>

### *Therapy/Management:*

Patients with XLI should have a thorough examination by a pediatrician. Referral to a dermatologist is indicated for topical emollient treatment. The best treatment, if tolerated, is to wear a plastic spacesuit as a pajama to bed after application of propylene glycol (40-60%) in water to the entire body. The patient should do this very night until the excess scales come off (usually 5-7 nights) and then as needed. Once-a-week use of the suit can keep skin clear.

If the patient is symptomatic or cryptorchidism is present, a pediatric urology referral is indicated.<sup>6</sup>

## **Lamellar Ichthyosis**

### *Description and Epidemiology:*

Lamellar means arranged in multiple layers or plate-like.<sup>3</sup> This ichthyosiform disorder is characterized by large (5 to 15mm), grayish brown scales that are quadrilateral in shape. They are adherent in the center and free at the edges.<sup>5</sup> Lamellar Ichthyosis (LI) is inherited as an autosomal recessive trait. It is a rare occurrence with an incidence of approximately 1:200,000 to 300,000 live births. The onset of LI is at birth.<sup>2-6</sup>

### *Pathogenesis:*

LI is due to mutations in the transglutaminase 1 gene.<sup>2-4, 19, 20</sup> Transglutaminases are a large group of enzymes that catalyze transamination of glutamine residues. This is necessary in a variety of processes including blood clotting, cytoplasmic destruction of the skin cells (apoptosis), formation of hair follicles, fertilization, and keratinization of skin.<sup>3</sup> Transglutaminase controls the cross-linking of cell envelope precursor proteins.<sup>3, 4, 21</sup> The LI phenotype is proposed to result from the incomplete cross-linking of these precursor proteins, producing an abnor-

mal cell envelope.

Ultrastructurally, this is supported by the fact that LI displays a thin or absent cell envelope.<sup>4, 22</sup>

At least three gene loci have been found for transglutaminase.<sup>3</sup> The specific transglutaminase 1 genes are heterogeneous chromosomes 14q11 and 2q33-35.<sup>4, 5, 6, 20</sup>

### *Clinical Aspects:*

Children who have LI usually present with a collodion-like membrane that encases the baby at birth. This membrane usually desquamates over the first 2 to 3 weeks of life. The scales with LI are large, thick, grayish-brown in color, and affect the entire cutaneous surface. In severe cases, the scales may be so thick that they are like armor plates.<sup>2-6</sup> Moderate hyperkeratosis of the palms and soles is frequently present. The follicles in most instances have a crateriform appearance.<sup>5</sup>

Ectropion (turning out of the lower eyelid) is almost always present with LI and is a helpful diagnostic sign. The red rim of the ectropion along the lower eyelid is distinctive and gives the eyes a constant "rheumy" look. Facial tautness is accentuated by eyelids and lips that are pulled out, corneal drying and attendant problems. The hair becomes matted down and sparse, and the nails can be dystrophic. Sweat ducts are obstructed and can lead to hyperpyrexia in hot climates or during exercise. Patients often have profound hypohidrosis and their potential for heat shock can be high.<sup>23</sup>

Because the skin is inelastic, fissures develop over the joints causing painful opening and superficial skin infections. In some cases, contracture deformities of the joints occur.<sup>2</sup>

### *Laboratory:*

The histopathology of LI shows hyperkeratosis and a markedly thickened granular layer, in contrast to the diminished granular layer of IV. Research laboratories have in vitro assays for transglutaminase 1 on fresh skin sections. Electron microscopy is useful in detecting the presence or absence of the marginal band.<sup>3</sup>

### *Prognosis:*

LI is a lifelong condition with little change. It does not affect intellect or lifespan. Once the psychological effects of altered body image are overcome, there is no reason that patients cannot be contributing members of society.<sup>3</sup>

### **Therapy/Management:**

Topical therapy with aggressive moisturization to keep the skin plasticized is the mainstay of treatment. Alpha hydroxy acids, urea-based creams, and propylene glycol can be used.

Applications are needed several times daily. Remember that the neonate has a high surface area to volume ratio and absorption of total body application of acid-based creams can cause systemic acidosis. In systemic treatment, oral retinoids provide marked relief for LI. They help relieve the thick scale, but they do not change the underlying pathology. Side effects of long-term retinoid use and issues of teratogenicity prohibit unrestricted use. Only physicians who are well acquainted with their risks and benefits should prescribe oral retinoids.<sup>3,6</sup>

## **Congenital Ichthyosiform Erythroderma**

### **Description and Epidemiology:**

Congenital Ichthyosiform Erythroderma (CIE) is also known as Nonbullous CIE.<sup>2,6</sup> It has a presentation of fine white scales over the entire body with widespread erythroderm of variable intensity.<sup>4</sup> Patients with CIE are often born as collodion babies and may initially be indistinguishable from infants with lamellar ichthyosis (LI).<sup>1</sup> CIE is an autosomal recessive ichthyosis with an unknown gene locus. It has an incidence of 1:180,000 live births. It is more common than LI, and there is an equal male to female ratio. The onset of CIE is at birth.<sup>4,6</sup>

### **Pathogenesis:**

The exact pathogenesis of CIE is unknown. There is an accelerated epidermal turnover rate with increased n-alkanes. This was previously thought to play a role, but has been found to be secondary to exogenous emolliation.<sup>6</sup>

### **Clinical Aspects:**

Most infants with CIE are born enclosed in a constricting parchment-like or collodion-like membrane that limits motion. Within 24 hours the skin begins to fissure and peel with large keratinous lamellae being cast off in 10 to 14 days. The underlying skin reveals redness and scales.<sup>5</sup> During infancy these patients develop generalized erythroderma with fine, white scales over the entire body. Generalized involvement is the rule, including face, palms, soles, and flexures. The legs may show large plate-like scales, but the rest of the body displays the characteristic fine, white scales. The hair has cicatricial alopecia and nail dys-

trophy may also be present.<sup>4,5,6</sup> The eyes, like LI, often show ectropion and eclabion.

### **Laboratory:**

When compared to LI, CIE has a more striking parakeratosis. Radioactive labeling indices of >15% clearly delineate CIE as a hyperproliferative keratosis and separate it from LI, which displays normal kinetics.<sup>24</sup> Ultrastructurally, CIE displays many distinctive features.

The epidermis has numerous lipid droplets in the corneocytes with large numbers of small lamellar bodies that have abnormal dimensions and basic unit patterns. The increased lamellar bodies of CIE are characteristic of hyperproliferative disorders and are another distinguishing feature.<sup>4</sup>

### **Prognosis:**

CIE usually has an unremitting course but it may improve at puberty.<sup>6</sup>

### **Therapy/Management:**

The newborn with CIE needs to be transferred to the neonatal intensive care unit. They need to be monitored for fluid status, electrolyte stability, and sepsis. A high-humidity chamber or maintaining a humid environment in the isolette is necessary. Simple emollients are safest during the exfoliative stage for the newborn and the use of keratolytics should be avoided.

For the older child or adult, the treatment of CIE is the same as LI. It consists of emollients, retinoids, and keratolytics. Additionally, calcipotriol has been shown to enhance differentiation, but does not reduce proliferation.<sup>3,4,6</sup> In a high turnover ichthyosis like CIE, one should monitor for anemia and treat with iron supplements if iron deficient. In kids that are failing to thrive and erythrodermic, the protein in their diet should be increased.<sup>6</sup>

## **Epidermolytic Hyperkeratosis**

### **Description and Epidemiology:**

Epidermolytic Hyperkeratosis (EH) is also known as bullous congenital ichthyosiform erythroderma.<sup>2-6</sup> Onset is evident at birth or soon thereafter with blistering and erythroderma.

When ruptured, the blisters leave tender denuded skin that is commonly infected with streptococcus or Staphylococcus aureus. EH is an autosomal dominant disorder of cornification.

It has a prevalence of 1:100,000-300,000. At least 50% of cases of EH are

sporadic and are thought to represent new mutations.<sup>4</sup> There is linkage to chromosome 12q and 17q, along with Keratin K1 and K10 gene mutations. There is an equal male to female ratio.<sup>6</sup>

### **Pathogenesis:**

EH is due to an error in synthesis of the epidermal keratins 1 and 10 which are found in the upper spinous to granular layers. The phenotypes differ slightly depending on the defect, with keratin 1 defects causing palm and sole bullae. The intraepidermal blistering seen in EH is due to abnormal keratin filament formation that leads to an abnormal cytoskeleton, resulting in mechanical fragility. In addition, the desmosomal attachments are imperfect, which leads to blister formation.<sup>4</sup>

### **Clinical Aspects:**

Newborns present with red, scaly lesions, widespread bullae, erythroderma, and areas of denuded skin. The blisters are superficial (in the upper epidermis) and, therefore, do not scar. Neonatal hyperkeratosis may be present, but it can be subtle. After the neonatal period, the blistering lessens (but does not disappear), and the hyperkeratosis becomes more obvious. The scale in EH is a distinctive porcupine-like quill that is thickened, horny, warty and ridged involving the entire body. These thick, grayish brown, sometimes verruciform scales prominently involve the flexures and the intertriginous areas. These areas are especially prone to excessive moisture and maceration, which lead to chronic bacterial overgrowth. This colonization produces a foul odor that is often quite distressing to the patient. Other parts of the skin may be involved, but to a lesser extent. There is remarkable heterogeneity, particularly in regard to extent of body surface involvement, presence or absence of erythroderma, and palm and sole involvement. Nails may be dystrophic and hair is normal.<sup>3,4,5</sup>

There are several variants of EH: bullous ichthyosiform erythroderma of Frocq, ichthyosis hystrix Curth-Macklin type, and ichthyosis bullosa of Siemens. Bullous ichthyosiform erythroderma of Brocq is the classic form of EH described above. Ichthyosis hystrix Curth-Macklin type may resemble EH both clinically and histologically, but it does not display blistering.<sup>4</sup> Several advances have been made in defining ichthyosis bullosa of Siemens as a distinct entity. Clinically, it resembles EH, but the hyperkeratosis is milder and generally confined to the extremities.<sup>4</sup> This condition is characterized by a lack of erythema, the "masering phenomenon"

(a superficial molting or peeling of the skin), and confinement of the epidermolytic change to the superficial layers of the epidermis.<sup>5</sup>

### Laboratory:

The histologic picture of EH is distinctive, but not pathognomonic. Hyperkeratosis is marked.

The granular layer is markedly thickened and contains coarse keratohyaline granules. Epidermal cells detach in the granular cell layer. EM reveals the formation of perinuclear haloes. These findings allow prenatal diagnosis by fetal skin biopsy.<sup>5,25</sup>

### Prognosis:

EH is a lifelong condition with a normal life expectancy. Generalized involvement may improve to localized disease after puberty.<sup>3,6</sup>

### Therapy/Management:

Newborns who exhibit bullae can have problems with fluid and electrolyte imbalances as well as sepsis. They should be managed in the intensive care unit with IV broad-spectrum antibiotics until cultures are negative, gentle handling to prevent further blistering, and protective isolation. Beyond the neonatal period, hyperkeratosis and foul odor are the two primary problems. Simple soaking in water, scrubbing, and after-bath greasing can soften

and remove many quills. Topical retinoic acids and/or alpha-hydroxy acids (10% glycolic acid lotions) are helpful, but the large body surface areas that must be treated and expense make these therapies prohibitive. Topical propylene glycolic (10% to 50% in water) is a less expensive alternative. It is applied under occlusion if possible, and the saturated scales fall off in the next bath. Use of oral retinoids is associated with mixed results; sometimes blistering is increased while scale is decreased. Avoid chronic oral antibiotics to prevent growth of resistant organisms. Emolliation and control of odor with antibacterial medication are the mainstays of therapy.<sup>3,6</sup>

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# Disseminated Cryptococcosis in AIDS

Igor Chaplik, D.O. St. Barnabas Hospital. Chief Resident Dermatology  
Dr. Charles Gropper, M.D. St Barnabas Hospital. Chief of Dermatology  
Dr. Cindy Hoffman, D.O. St Barnabas Hospital. Dermatology Program Director  
Dr. Richard Hwang, M.D. St. Barnabas Hospital. Staff Pathologist.

*Cryptococcus Neoformans* is an opportunistic pathogen that frequently presents with skin findings. Pulmonary complaints coupled with signs of disseminated disease, such as skin or CNS findings should alert the physician to the possibility of cryptococcosis. One such patient is presented, along with the diagnostic, therapeutic, and prognosticating factors that influence decision making in such patients.

*Cryptococcus neoformans* is an encapsulated yeast like fungus. Strains are grouped into two varieties that include five serotypes known as *C. neoformans* variety *neoformans* (serotypes A, D, and AD) and *C. neoformans* variety *gattii* (serotypes B and C). The serotype differences reflect antigenic differences in the structure of the capsular polysaccharide. *C. neoformans* var. *neoformans* is found throughout the world in association with excreta from certain birds including pigeons, chickens, canaries, and cockatoos, as well as contaminated soil, fruits, and milk<sup>1</sup>. *C. neoformans* var. *gattii* is found primarily in tropical and subtropical regions and has been associated with several species of eucalyptus trees. In order to cause disease in humans, the fungus must be inhaled into the lungs, although a small percentage of patients can develop primary cutaneous cryptococcosis after direct implantation.<sup>2,3</sup>

## Case Report

A forty one year old African American male was admitted to the hospital for fever, cough, groin swelling, and an asymptomatic skin rash for the last three months. He is an intravenous heroin drug abuser and is presently homeless. His immune status and past medical history is unknown, he denies allergies to medicine, and is presently not taking medication. He has received cryotherapy for his rash at a local clinic. Upon further questioning, the patient admits to intermittent headaches, weakness, shortness of breath, and a twenty-pound weight loss over the last month.

The physical exam revealed a cachectic, febrile patient with a temperature of 102.4°F. He was breathing rapidly at 22 breaths per minute, and his heart rate was 76. His blood pressure was 90/66. His skin exam revealed several, discrete, dome-shaped, some umbilicated, papules on the abdomen and chest. Also present were several, hyperpigmented, scaly plaques on his abdomen and chest. (Fig. 1 and 2). Bilateral inguinal and axillary lymph nodes were palpable. Auscultation

of the lungs revealed bilateral rales and rhonchi.

Due to the constellation of findings, an HIV test was performed, a PPD placed, a full sepsis work-up initiated, and a skin biopsy performed. The working differential diagnosis was that this patient was immunocompromised and that a community acquired pneumonia, tuberculosis, or an opportunistic pathogen were causing his symptoms. The dermatological presentation coupled with systemic findings adds to the possibility that an organism that causes molluscum-like lesions such as *Histoplasma capsulatum*, *Coccidioides immitis*, *Penicillium marneffeii*, or *Cryptococcus neoformans* had disseminated to the skin and possibly other organs.

Subsequently, the patient was placed on empiric treatment with intravenous fluconazole, ceftriaxone, azithromycin, and fluid replacement. The patient's complete blood count revealed a white count of 8600, with 84.9% neutrophils. His hemoglobin was low at 10.2 g/dl and his hematocrit low at 31.1%. The patient was found to be HIV positive, with a CD4 < 20 cells/microliter and an RNA by PCR of 69965 copies/ml. His skin biopsy revealed numerous organisms of various sizes surrounded by capsules, which stained positive with mucicarmine in the superficial and deep dermis, with very little inflammatory response. (Fig 3,4) His Chest X-ray and CT scan revealed bilateral pulmonary infiltrates suggestive of septic emboli vs. malignancy and mediastinal and hilar adenopathy. His blood culture grew out a fungus, which was later identified to be *Cryptococcus neoformans*. Also, the patient's serum was positive for cryptococcal antigen at a titer of 1 to 4096. Furthermore, a CT scan of the brain with contrast showed nonenhancing hypodensities in the right thalamic nuclei, corpus callosum, and right occipital lobe. A CSF analysis was subsequently obtained and revealed an elevated protein of 53 mg/dl, no WBC's, and 19 RBC/mm<sup>3</sup>. The CSF fluid was positive for an India ink preparation and the CSF culture also grew *Cryptococcus neo-*

*formans*. A lymph node biopsy revealed massive amounts of organisms that expand nodal sinuses and stain positive with mucicarmine. (Fig 5) During the course of his hospitalization, the patient became hypoxic and a bronchoscopy with alveolar lavage was performed. The patient's lavage specimen contained numerous organisms that stained positive with mucicarmine, and grew out *Cryptococcus neoformans* and *Aspergillus fumigatus*. (Fig. 6) Despite the addition of intravenous amphotericin B and ventilatory support, the patient succumbed due to respiratory failure and overwhelming cryptococcal infection.

## Comment

When *Cryptococcus* is inhaled through the lungs, the infection is either entirely cleared by the host, becomes dormant, or becomes an acute infection that may systematize. The direction and outcome of the infection depends on the complex interplay between the immune system, the virulence of the fungus, and the size of inoculum. The host's immune status appears to be the most important factor in determining outcome and a healthy host is usually able to contain the fungi with a brisk and effective immune response. This response relies mostly on T-cell mediated immunity and granulomas are formed to wall of the infection, similar to the primary complex seen *Mycobacterium tuberculosis*.<sup>4,5</sup> Because HIV predominantly infects T cells, fungemia and subsequent dissemination is strikingly common in the compromised host, particularly when the T helper count falls below 100 cells/micrometer.<sup>5</sup> In fact, several studies show that even those who are directly exposed to *C. neoformans*, such as healthy lab workers in cryptococcosis research facilities, rarely develop symptomatic infection despite testing positive on delayed hypersensitivity skin tests.<sup>6</sup> An immunocompromised host, as in this case, is much more likely to develop acute and chronic infection. Rates of cryptococcosis in non-HIV patients approach 1 in 100,000<sup>7</sup>, whereas cases in HIV infected patients approaches as high

as 13.3%<sup>8</sup> in some large U.S. cities. Patients with cancer<sup>9</sup>, organ transplants<sup>10</sup>, chronic steroid therapy<sup>11</sup> systemic lupus erythematosus<sup>12</sup>, and multiple myeloma<sup>12</sup> are also at an increased risk of developing disease. Co-infection with other pathogens is not uncommon and was a factor in the patient presented. Although there is no characteristic x-ray finding, single or multiple nodules are the most commonly encountered and are often confused with tumor.<sup>13</sup> Radiographic findings of single or multiple nodules, mass-like infiltrates, pleural effusions, cavitation, and hilar adenopathy have all been reported.<sup>13</sup>

From the lungs the fungus can infect any organ system via the bloodstream, the skin being the second most common site.<sup>5</sup> Cryptococcal dissemination to the skin occurs in 10-20% of patients and is often the presenting sign of disease.<sup>14</sup> Cutaneous manifestations of disseminated disease are protean and most commonly occur on the head and neck.<sup>15</sup> Although molluscum-like lesions are the most common; acneiform lesions, purpura, vesicles, tumors, abscesses, oral and genital ulcers, granulomas, plaques, sinus tracts, cellulitis, subcutaneous nodules, and HSV-like lesions have all been reported.<sup>14,16,17,18,19</sup> Direct cutaneous cryptococcosis caused by traumatic implantation is rare and produces solitary nodules that ultimately break down or ulcerate.<sup>3,6</sup> Lymphadenopathy may or not be present. Biopsy specimens will often show two types of histological patterns: gelatinous and granulomatous. This patient's biopsy consisted of the gelatinous type, which produces little inflammatory reaction and numerous organisms (4 to 12 µm) with large polysaccharide capsules.<sup>20</sup> The capsule stains purple with methylene blue, blue with alcian blue, and red with mucicarmine.<sup>20</sup> The granulomatous type produces more of an inflammatory reaction with giant cells and a small number of organisms. The organisms are 2 to 4 µm, have thin or no capsules, and are found within giant or mononuclear cells. The fungi stain red with PAS, black with methanamine silver, and dark brown with Fontana-Masson.<sup>20</sup> A large majority of patients who have confirmed cutaneous cryptococcal disease do so as a result of dissemination. As such, a thorough work-up for organ involvement, particularly the CNS, is indicated.

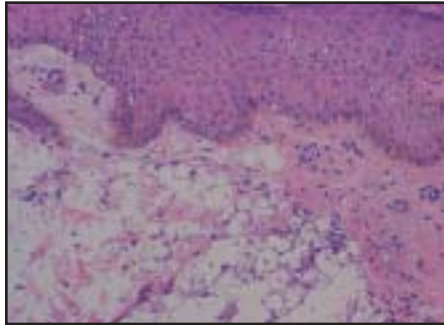
The CNS is the most common site of dissemination and any immunocompromised patient that has evidence of lung or skin cryptococcosis should have a lumbar puncture to rule out CNS disease.<sup>5</sup> According to one series, 90% of AIDS patients with cryptococcal pneumonia have concomitant CNS dissemination at



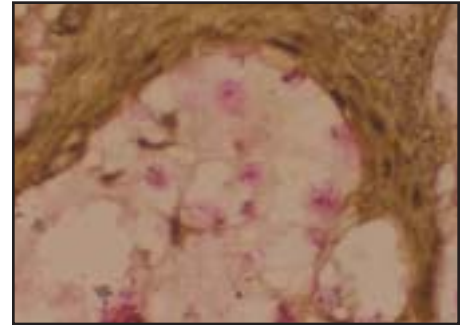
**Fig. 1 showing numerous, discrete, dome-shaped, some umbilicated papules and several, fairly well-defined, hyperpigmented, scaly plaques on abdomen and chest.**



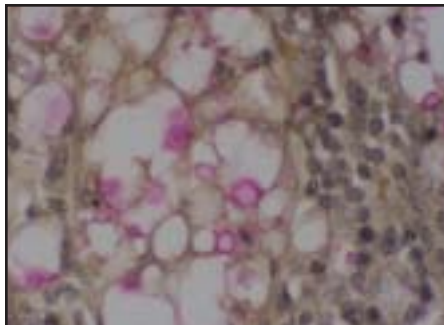
**Fig. 2 Close-up of umbilicated papule.**



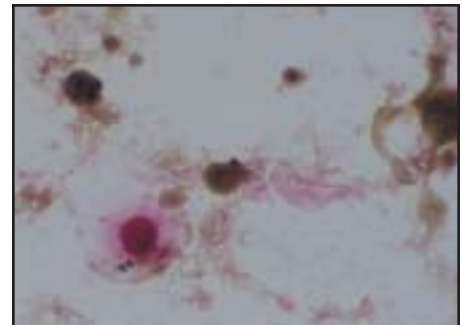
**Fig 3. H & E stain of 3mm punch biopsy at 10X showing numerous encapsulated organisms in the superficial and deep dermis with very little inflammatory response.**



**Fig. 4. Mucicarmine stain of 3mm punch biopsy at 40X showing the characteristic red staining capsule in the superficial dermis.**



**Fig 5. Mucicarmine stain showing a 40X of lymph node revealing large amounts of red staining organisms that expand nodal sinuses.**



**Fig 6. Mucicarmine stain of alveolar lavage showing 40 X organism stained red with mucicarmine in proximity to alveolar macrophage.**

time of presentation.<sup>12</sup> A culture of CSF fluid, fluid analysis, and opening pressure are imperative to the diagnosis, management, and prognosis of disease. Because high CSF pressures are discovered in over 50% of AIDS patients and may lead to a worse prognosis, some authors recommend serial lumbar taps and shunts to both monitor and maintain normal pressure.<sup>21</sup> Also, the direct examination of CSF using an India ink preparation can yield a rapid diagnosis and was positive in this patient. CT scans and

MRI can also be used to diagnose and manage CNS disease. On radiography there is no pathognomonic finding, but hydrocephalus, gyral enhancement, and single or multiple enhancing and nonenhancing nodules (as in this case) have all been reported.<sup>22</sup>

Because opportunistic cryptococcal fungemia spreads in a characteristic way to organ systems, diagnostic tests should be tailored based on signs and symptoms. Hemotogenous seeding is particu-

larly high in the immunocompromised and a blood culture is essential in determining cryptococemia, turning positive in 3-7 days.<sup>5</sup> A more rapid approach, that is both specific and sensitive, is the serologic detection of cryptococcal polysaccharide capsule using either latex agglutination or enzyme immunoassay. In fact, the antigen can be detected in urine and CSF fluid as well. A urine culture is necessary to rule out prostatic involvement. The prostate has been described as a reservoir for relapse of infection even during antifungal treatment.<sup>23</sup> An ophthalmologic consult is warranted because eye involvement can lead to loss of vision, retinal involvement, cranial palsies, and endophthalmitis. Presenting signs in organ systems such as skin and lymph nodes often prompt biopsies and can lead to the diagnosis before cultures become positive. Furthermore, a KOH preparation, Tzanck smear, and India ink preparation of any tissue suspected of harboring fungi may also be used as a rapid, direct test for diagnosis

The treatment approach after the diagnosis is established in a patient with AIDS relies on Amphotericin B. Although amphotericin B monotherapy for the treatment of cryptococcal meningitis is proven to improve survival, combination therapy with flucytosine allowed for lower Amphotericin doses at shorter courses and less toxicity.<sup>25,26,27</sup> Among patients with HIV infection and cryptococcal meningitis, induction therapy with amphotericin B (0.7-1 mg/kg/d) plus flucytosine (100 mg/kg/d for 2 weeks) followed by fluconazole (400 mg/d) for a minimum of 10 weeks is the treatment of choice.<sup>28</sup> Fluconazole should be continued for life. Lipid formulations of amphotericin B can be substituted for amphotericin B for patients whose renal function is impaired. Ambisone at 4 mg/kg/day has been shown to perform similar to Amphotericin B.<sup>29</sup> For those patients with HIV who present with isolated pulmonary, cutaneous,

or urinary tract disease, fluconazole (200-400 mg/d) is indicated and itraconazole (200-400 mg/d) is an acceptable alternative.<sup>29</sup> For immunocompetent hosts with pulmonary disease, non-CNS-isolated cryptococemia, urinary tract or cutaneous disease, fluconazole for 3-6 months is the drug of choice.<sup>28</sup> Itraconazole (200-400 mg/day) for 6-12 months is an acceptable alternative.

The treatment of disseminated disease in AIDS has been clearly delineated and shown to improve morbidity and mortality. Prognosis, however, depends most on control of the patient's underlying disease and may be poor despite adequate treatment. Patients with high polysaccharide antigen titers (>1:1024), heavily positive India ink examination, weak CNS response to infection (<20 leukocytes/microliter), and altered mental status show a high fungal burden and tend to do poorly.<sup>5</sup> Rapid diagnosis leading to proper treatment will improve survival in most patients with cryptococcosis. Because cryptococcosis often manifests with skin findings coupled to systemic disease in the immunocompromised patient, a high index of suspicion for this opportunistic pathogen must be maintained.

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# Necrolytic Migratory Erythema in a Patient with Glucagonoma - A Case Report

Lynn M Sikorski, D.O., Michael Eyre, D.O., Ryan J Seaman, D.O.

## Case Report

### History of Present Illness

A 34-year-old Caucasian male presented to the dermatology department with a six-week history of a painful, pruritic groin rash. The rash began on the upper, inner thighs and then slowly progressed to include the scrotum and base of the penis. He described the rash as being initially pruritic, but recently becoming painful as to make daily washing painful and walking difficult.

The patient also complained of red patches on his face and scalp with associated scale. He denied any dysuria, hematuria or penile discharge. Other than occasional diarrhea, he denied any constitutional symptoms. He could not recall any history of a similar rash. Previous trials of antifungal and corticosteroid creams proved unhelpful.

Upon further questioning, the patient stated he had previously been treated with somatostatin infusions for a tumor of the pancreas. He independently stopped infusions three months prior to presentation at our clinic. He also reported taking several anti-depressant medications (Remeron, Wellbutrin and Zyprexa) for the past eight weeks. Recently, Trazadone had been added to his psychiatric regimen.

### Physical Exam

Physical exam revealed a 34-year-old cachectic white male with a flat affect. Diffuse and patchy erythema with scale was noted on the scalp, face and bilateral palms. The scalp hair appeared thinned and brittle. Erythema and fissuring were noted at the oral commissures. The tongue was erythematous and enlarged with lateral imprints of dentition (Fig. 1-4). Sclera were anicteric and no hepatosplenomegaly was appreciated. Beefy red, erosive patches with surrounding erythema were noted on the scrotum, base of the penis and upper medial thighs (Fig. 5-6).

### Laboratory

Laboratory investigation showed a normochromic/ normocytic anemia (hemo-

globin 13.0 G/DL, normal 14-18). ALT was elevated (74 IU/L, normal 7-40) along with alkaline phosphatase (195 U/L, normal 37-107). PTH, intact PTH, serum calcium, total protein and zinc were all within normal limits. Elevated hormones included insulin (27.5 U/L, normal 1-18), gastrin (112 PG/L, normal 0-90) and glucagon (1650 NG/L, normal 40-130). A pathological specimen was not obtained. Computed tomography (CT) of the abdomen revealed calcification of the tail of the pancreas (Fig. 7) with multiple metastatic lesions in the liver (Fig. 8).

### Management

With the diagnosis of necrolytic migratory erythema in association with glucagonoma syndrome, the patient was referred to oncology. A regimen of alternating streptozocin and adriamycin was started. Repeat imaging, performed after three cycles of chemotherapy, revealed stabilization of the pancreatic and liver masses. Laboratory testing revealed near normalization of serum glucagon levels. Resolution of skin findings was achieved with a mixture of nystatin, hydrocortisone and zinc oxide. The patient showed an increase of thirty-five pounds over three months of chemotherapy. Psychiatric medications were continued as before.

### Discussion- Glucagonoma

Necrolytic Migratory Erythema (NME) is seen in paraneoplastic syndromes resulting from gastroenteropancreatic (GEP) tumors. The most common tumor associated with NME is a glucagonoma. Glucagonomas make up approximately 2% of all malignancies of the gastrointestinal system, with an increasing incidence in the United States over the past two decades<sup>(12)</sup>. Tumors of the gastroenteropancreatic system may present with a mixture of hormone overproduction in 30% of cases, usually with a dominant hormone<sup>(14)</sup>. Characteristic dominant-hormone tumors are seen in several syndromes such as Carcinoid (serotonin), Zollinger-Ellison (gastrin), Insulinoma (insulin), Verner-Morrison (vasointestinal peptide), Somatostatinoma (somatostatin), and Glucagonoma (glucagon).

Accounting for 4% of all GEP tumors,



Fig. 1



Fig. 2



Fig. 3

the estimated incidence of glucagonomas is 1 in 20 million per year with only 200 published cases to date<sup>(3)(4)</sup>. It is usually seen in the 4th and 5th decades with an equal female to male preponderance.



Fig. 4



Fig. 5



Fig. 6

Occasionally, it may be part of multiple endocrine neoplasia (MEN) syndromes, especially MEN1 where 13% of such patients may be affected<sup>(13)</sup>. In such cases, the patient is usually less than 40 years old and there are associated parathyroid tumors and pituitary hyperplasia.

### Presentation

The clinical presentation of the glucagonoma syndrome is varied. Weight loss is the most common presenting sign, seen in 73% of patients. Following weight loss is the characteristic rash termed necrolytic migratory erythema<sup>(15)</sup>. Diabetes mellitus may also be present. In

most cases, there are factors beyond the increased glucagon leading to diabetes. These include pre-existing insulin resistance, secondary hormones, metabolic changes due to the primary tumor burden or metastases and side effects of chemotherapy<sup>(4)</sup>. Other than cheilosis or stomatitis, gastrointestinal complaints are usually limited to diarrhea<sup>(5)</sup>. Rarely, abdominal pain may be present.

Patients may also be anemic. This is usually a normochromic/ normocytic anemia, but it may be macrocytic in some. Neurological changes, a characteristic feature of all GEP tumors, are present in 20% of patients (14). The changes are varied and include depression, dementia, psychosis, optic atrophy, incontinence and muscle weakness. In contrast to the neurological changes seen in many of the GEP tumors, thromboembolic phenomena are unique to glucagonoma syndrome. Seen in nearly 30% of patients, thrombosis accounts for more than 50% of deaths reported<sup>(4)</sup>.

### Diagnosis

Diagnosis of the glucagonoma syndrome relies on several sources. No test or symptom is individually diagnostic. In addition to the classical clinical presentation of NME along with diabetes mellitus and weight loss, elevated serum glucagon and radiologic evidence of pancreatic tumor are helpful for diagnosis. A serum glucagon greater than 1,000 NG/L is highly suggestive of existing glucagonoma. However, a normal response cannot rule out the presence of an islet cell tumor of the pancreas. On the other hand, one may see an increased glucagon without an associated rash of NME. Secondary hyperglucagonemia usually presents with levels less than 500 NG/L<sup>(14)</sup>. The differential of such cases is large and includes liver disease, pancreatic disease, chronic renal failure, myocardial infarction, fasting or starvation, diabetes mellitus, bacteremia or sepsis, celiac disease, trauma, burns, surgery, Cushing's syndrome and danazol therapy.

Diagnosis of glucagonomas has been aided by several advancements in radiologic imaging. Most of the tumors are found in the pancreas, 50% being found in the tail. Rarely, they may be found in extra-pancreatic tissues such as the duodenal wall and kidney<sup>(12)</sup>. Computed tomography is the most common method of imaging, but selective visceral angiography may be the gold standard. Angiography allows better visualization of these hypervascular tumors and will show hepatic metastases despite a normal liver scan.



Fig. 7

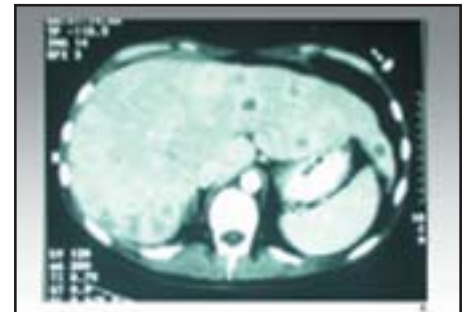


Fig. 8

### Therapy

Once diagnosed, therapy consists of medical and, at times, surgical intervention. Surgery is the optimal treatment modality; however, because of the multicentricity of primary tumors, the high rate of co-morbidities and usual delay in diagnosis, surgical extirpation is usually only palliative. Glucagonomas are slow growing and often encapsulated, allowing for surgical debulking. Palliative surgeries have shown a considerable decrease in morbidity in some cases. Perioperative management is complicated by the increased risk of thrombosis, poor control of blood glucose levels, need for transfusions and delayed wound healing secondary to a relative decrease in amino acids. Survival rates are not enhanced by surgical therapy<sup>(4)</sup>.

Medical therapy may be employed in combination with palliative tumor debulking, or alone when surgery is not possible. Options include pharmacologic and cytotoxic chemotherapy and supplementation with amino acids, zinc and essential fatty acids. Pharmacologic therapy consists primarily of the synthetic analog of somatostatin called octreotide (Sandostatin). By inhibiting pituitary and gastrointestinal hormones, octreotide increases absorption of water and elec-

trolytes, decreases pancreatic and gastric secretions and delays intestinal transit time. Octreotide is limited, however, by a short plasma half-life of 3 to 4 minutes. Newer somatostatin analogues such as Lanreotide or Octreotide long acting repeatable (LAR) may prove to be more useful. Lanreotide has a biological activity of 10 to 14 days, allowing the suppression of symptoms to last for 7 to 10 days<sup>(16)</sup>, while Octreotide LAR was found in an Italian study to alleviate symptoms for 28 days at a time<sup>(11)</sup>. While it may improve symptomatology, these somatostatin analogues do not, however, lead to suppression of tumor growth.

Alternative therapies include hepatic artery embolization and transplantation. Embolization, while never curative, may reduce tumor mass, control symptoms of hormone excess and prolong life<sup>(15)</sup>. Total pancreatectomy with liver transplantation has been reported. This may be an option, but only in cases diagnosed early in patients with minimal co-morbid conditions.

### Prognosis

Because of varied and insidious presentations, the morbidity and mortality rates are rather high in cases of glucagonoma syndrome. Metastatic disease is present in 50-75% of patients. Liver metastases (80%) are seen most commonly, followed by the peripancreatic lymph nodes (38%)<sup>(9)</sup>. Other areas of metastases include bone, lung, adrenals, kidney and chest wall. Tumor-related death averages 3-7 years and is usually a result of thromboembolism, sepsis or gastrointestinal bleeding.

### Discussion-Necrolytic Migratory Erythema

First described in 1942 by Becker, NME is the hallmark of glucagonoma syndrome<sup>(3)</sup>. The rash is seen in approximately two-thirds of patients and usually begins as small, erythematous macules and papules in the perineum, lower extremities and periorificially. Lesions tend to coalesce and blister with central erosions. Healing may leave an indurated bronze discoloration<sup>(4)</sup>. Affected areas are regularly pruritic and often intensely painful. Secondary infections like candida and staphylococcus may be present.

Most cases of NME secondary to glucagonoma follow Curth's criteria for diagnosing a paraneoplastic syndrome. First, both conditions begin simultane-

ously and follow a parallel course. Neither symptom, nor their correlation is explained by a genetic etiology. This specific, uncommon dermatosis occurs with this specific tumor, and the association of the two conditions occurs in a high percentage. Along with the fact that symptoms of NME are frequently relieved following treatment of the tumor, NME is most often considered to be a paraneoplastic phenomenon<sup>(6)</sup>.

### Differential Diagnosis

Because of slow onset and varied presentation, NME may be difficult to diagnose. Similar appearing rashes include acrodermatitis enteropathica, Seborrheic dermatitis, subcorneal pustular dermatosis, psoriasis, contact dermatitis, Hailey-Hailey disease, pemphigus foliaceus, paraneoplastic pemphigus, pellagra and mucocutaneous candidiasis<sup>(1)</sup>.

### Pathophysiology

The exact mechanism producing NME is unknown, but several theories have been put forth. Some investigators propose that, because of the excess glucagon, patients exist in a catabolic state. This leads to prolonged gluconeogenesis and glycogenolysis with subsequent depletion of epidermal proteins. Ultimately, epidermal necrosis develops<sup>(2)</sup>. Other possible mechanisms that may be responsible for NME have to do with the liver. Because of frequent hepatic involvement, there may be decreased amino acids, zinc and essential fatty acids<sup>(7)</sup>. Each of these may independently lead to keratinocyte toxicity<sup>(14)</sup>. Striking similarities exist between the cutaneous findings in NME and acrodermatitis enteropathica, though serum zinc levels are inconsistently low in NME. Deficiencies in mononuclear and polymorphonuclear cell chemotaxis have been noted, which may be related to inappropriate zinc uptake, thus contributing to the dermatitis<sup>(3)</sup>.

### Histology

Although several different patterns may be seen, key features of NME include confluent parakeratosis, variable acanthosis, necrosis of the upper epidermis, edema of the papillary dermis with vascular dilation and a lympho-histiocytic infiltrate<sup>(7)</sup>. Immunofluorescent studies are negative.

### Therapy

Many therapies have been used to alleviate the symptoms of NME. Certainly, the best therapy is to cure or

lessen the effects of the underlying glucagonoma and accompanying biochemical abnormalities. Topical antifungals and antibiotics are useful in cases of secondary infections. Infusions of amino acids, essential fatty acids and zinc have proved to be beneficial in some cases; however, such therapy tends to be expensive<sup>(4)</sup>. Diet may be modified with caloric supplementation and high protein intake to offset the negative nitrogen balance brought about by the prolonged catabolic state. Other therapies that have been used include oral steroids, UV light, methotrexate and Dapsone<sup>(14)</sup>.

Overall management should include careful screening and monitoring for other endocrinopathies. Elevations in other hormones are common in GEP syndromes. In fact, elevated gastrin levels are seen in 50% of glucagonoma cases. Increased insulin is the next most common hormone abnormality<sup>(14)</sup>. Because of the near certainty of developing insulin-dependent diabetes mellitus, patients should be offered comprehensive diabetic counseling and education. Prompt referral should be made to oncology, neurology, endocrinology and psychiatry services.

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# Mastocytosis

Robert A. Norman, D.O., MPH, FAAD, Cynthia Futral-Eason, DO

## Abstract

*A literature review was performed to determine recent medical practices concerning the pathophysiology, diagnosis and treatment of mastocytosis. Literature was reviewed concerning the following conditions: urticaria pigmentosa, mastocytoma, diffuse erythrodermic mastocytosis, and telangiectasia macularis eruptiva perstans (TMEP). A representative sample of scientific papers included research from 1980 to the present time.*

## Background

Mastocytosis is due to the excess of normal-appearing mast cells in the skin. The three forms include urticaria pigmentosa, solitary mastocytomas, and diffuse cutaneous mastocytosis. The pediatric cutaneous form is the most common.

## History

The incidence is 1 in 1000 to 1 in 8000 live births. It is usually confined to the skin in young children, and adults are more likely to develop systemic forms. The cause is unknown. Familial occurrence is rare. The onset is between birth and 2 years in 55% of cases, an additional 10% of cases occur before age 15. The condition gradually improves and usually clears spontaneously by puberty. If the disease begins after age 10, it usually persists for the patient's life. If the disease is systemic, the gastrointestinal tract and the skeletal system are most commonly involved. Although itching is minimal with localized disease, it can be very bothersome with large numbers of lesions present.<sup>(1)</sup>

Urticaria Pigmentosa is the most common form of mastocytosis. It is characterized by small, reddish-brown macules or papules that occur mainly on the trunk of the body. They may range in number from a few to thousands<sup>(2)</sup>. These tend to urtication with mild mechanical trauma or chemical irritation. The lesions may then become pruritic, edematous and erythematous. This is referred to as Darier's sign. It is probably a result of mast cell degranulation induced by physical stimulation<sup>(3)</sup>.

The macules or papules in urticaria pigmentosa contain a large number of mast cells. Mastocytosis is characterized by mast cell proliferation and accumulation within various organs, most commonly the skin. Types of cutaneous mastocytosis include mastocytoma, diffuse erythrodermic mastocytosis, telangiectasia macularis eruptiva perstans (TMEP) and urticaria pigmentosa.<sup>(4)</sup>

## Pathophysiology

Mastocytosis is probably a hyperplastic

response to an unknown stimulus and not a neoplastic condition. There are rare cases recorded of familial urticaria pigmentosa<sup>(4)</sup>. Local concentrations of mast cell growth factor in skin lesions are postulated to stimulate mast cell proliferation, melanocyte proliferation, and melanin pigment production. This induction of melanocyte production explains the hyperpigmentation that is commonly associated with skin mast cell lesions<sup>(5)</sup>. Some forms of mastocytosis produce systemic manifestations. These are thought to be associated with the release of several mast cell derived mediators including: histamine, prostaglandins, heparin, neutral proteases, and acid hydrolases. These mediators can induce symptoms that may include: headache, flushing, dizziness, tachycardia, hypotension, syncope, anorexia, nausea, vomiting, abdominal pain, and diarrhea<sup>(6)</sup>.

Mastocytosis presents with a highly variable clinical picture. In urticaria pigmentosa lesions are multiple and widely distributed. The lesions are round to oval, red-brown, non-scaling papules and small plaques. In systemic mastocytosis, skin lesions similar to those seen in urticaria pigmentosa are accompanied by mast cell infiltration of bone marrow, liver, spleen, and lymph nodes<sup>(6)</sup>.

The histology of mastocytosis usually varies from a small increase in the numbers of spindle-shaped and stellate mast cells around superficial dermal blood vessels, to large number of tightly packed, round to oval mast cells in the upper to mid-dermis. This may also be accompanied by variable fibrosis, edema, and small numbers of eosinophils. Because of extensive mast cell degranulation, it is sometimes difficult to detect these cells with light microscopy without special metachromatic stains<sup>(5)</sup>.

Factors Associated with Urticaria Pigmentosa

Mortality/Morbidity: Most cases of urticaria pigmentosa in children resolve spontaneously. However, acute extensive mast cell degranulation can on rare occasions cause life-threatening shock.

Urticaria pigmentosa with onset occurring in adolescence or adulthood is more likely to produce a persistent condition and there is a greater risk of systemic involvement. Juvenile onset systemic mastocytosis has around a 7% malignancy transformation rate, while adult onset mastocytosis has up to a 30% malignant transformation rate<sup>(4)</sup>.

Race/Nationality: Most reported cases are in Caucasians. This may be because the cutaneous lesions characteristic of most type of mastocytosis are less visible in more pigmented skin. The incidence of mastocytosis does not appear to be different in other countries than in the United States<sup>(5)</sup>.

Gender/Age: Mastocytosis affects males and females equally. With regard to age, most affected patients are children. About 75% of all cases occur during infancy or early childhood. There is a second incidence peak in the 30's and 40's<sup>(4)</sup>.

## History and Physical

Patients commonly present with pruritic cutaneous lesions which may be extensive. Pruritus and flushing may be triggered by certain foods, temperature changes, alcohol and drugs such as morphine, codeine, and aspirin<sup>(5)</sup>.

Besides the skin manifestations, patients may experience flushing, headache, dyspnea, wheezing, rhinorrhea, nausea, vomiting, diarrhea, and syncope. It also possible for patients to have chronic systemic complaints involving various organ systems. These could include:

Skeletal system-bone pain or new onset of fracture

CNS-neuropsychiatric symptoms as well as malaise and irritability

GI-weight loss, diarrhea, nausea/vomiting and abdominal cramps

Cardiovascular-shock, syncope(from vascular dilation) or angina<sup>(3)</sup>.

Findings upon physical examination could possibly be variable and would

include one or some of the following:

Skin- lesion types--Macules, papules, nodules, plaques, blisters and bullae in children

Skin- distribution Widespread symmetric distribution, trunk more than extremities, usually not on face, scalp, palms, and soles. (a large solitary collection is called a mastocytoma)

Skin-color, number, size

Usually number from 1-1000, size 1mm-several cm., color yellow-tan to Red-brown, slightly elevated plaques, typically form in small groups on the trunk. Erythema and blisters (often after scratching) are common in the first two years of life.

Skin-special characteristics--Darier's sign, and dermatographism in uninvolved skin, flushing from stroking or after ingesting a mast cell degranulating agent

Liver- possible hepatomegaly(40% of adults with systemic mastocytosis)

Spleen- possible splenomegaly(50% of patients with systemic mastocytosis)

Cardiovascular- hypotension<sup>(5)</sup>

## Lab Studies

### *Skin Biopsy*

In many cases urticaria pigmentosa can be diagnosed by a history and physical examination revealing the characteristic lesions that demonstrate Darier's sign<sup>(3)</sup>. The most common confirmatory test is a skin biopsy. In the skin biopsy, an anesthetic agent without epinephrine should be injected adjacent but not directly into the lesion to be biopsied, so that mast cell degranulation can be avoided. It may be necessary to stain the biopsy with Giemsa stain in order to visualize the mast cell granules<sup>(5)</sup>.

### *Blood/Urine Tests*

In patients with systemic mastocytosis a CBC exam may demonstrate anemia, thrombocytopenia, leukocytosis and eosinophilia. With regard to urinalysis patients with extensive skin lesions may have a two to three time normal elevation in urine histamine excretion(based on 24 hour urine test)<sup>(4)</sup>.

## Imaging Studies

If a pediatric patient's CBC is abnormal then a bone scan and radiologic survey is normally done. The same is true of non-pediatric cases of systemic mastocytosis. Any patient who complains of problems with the skeletal system should also have a bone scan and radiologic survey to identify any bone lesions, osteoporosis, or osteosclerosis<sup>(3)</sup>. If a patient complains of GI problems then a GI workup should be ordered to identify peptic ulcers, abnormal mucosal patterns or motility disturbances.<sup>(6)</sup>

### Other Tests Useful in Diagnosing Mastocytosis

Serum Tryptase--Tryptase levels are elevated in mastocytosis. These levels may be more useful than histamine levels, because histamine can be elevated in hypereosinophilic states.<sup>(3)</sup>

NMH (Urinary N-methylhistamine)-NMH levels are more specific and sensitive than urinary histamine levels. NMH levels correlate directly with the extent of skin lesions. NMH levels decrease with age, so age must be taken into consideration when interpreting results.<sup>(5)</sup>

Urinary PGD2 Metabolite Level-Although this test is not widely available it is useful. Even during asymptomatic periods urinary PGD2 metabolites may range from 1.5-150 times above normal<sup>(6)</sup>

## Treatment

Medical therapy is conservative and focuses on symptomatic relief. The prognosis for most mastocytosis patients is very good, and none of the medicines currently available induce permanent involution of skin lesions or systemic involvement. Patients should be instructed to avoid medications that precipitate mast cell mediator release. These agents include: aspirin, NSAIDs, codeine, morphine, alcohol, thiamine, quinine, opiates, gallamine, decamethanonium, procaine, radiographic dyes, dextran, polymyxin B, scopolamine, and D-turbocurarine. Dietary substances that should be avoided are salicylates, crawfish, lobster, alcohol, spicy foods, hot beverages, and cheese.

Recognition and explanation of the disease helps parents limit unintentional

scratching and trauma of the lesions.

In addition patients should avoid stimuli such as high emotional stress, temperature extremes, physical exertion, bacterial toxins, and insect bites<sup>(7,8,9)</sup>.

### Medications Useful in Mastocytosis

H1 and H2 antihistamines are sometimes used to decrease pruritus, flushing, and GI symptoms. Oral disodium cromoglycate is useful in ameliorate cutaneous symptoms like pruritus, whealing and flushing, as well as systemic symptoms like diarrhea, abdominal pain, bone pain, and cognitive function disorders.<sup>(10)</sup>

If a patient does not respond well to H1 and H2 antagonist therapy then a very cautious administration aspirin is indicated. The aspirin can be slowly titrated to a plasma level 20-30mg/100mL. This treatment should be done with caution because aspirin can induce mast cell mediator release and subsequent cardiovascular collapse.<sup>(10)</sup>

Skin lesions that involve a limited body area may be treated with potent Class 1 topical corticosteroids. It is also possible to do intralesional injections of dilute corticosteroids. Skin atrophy and adrenocortical suppression can be minimized by treating limited body areas during a single treatment session. Generally, systemic corticosteroids are not useful for mastocytosis except where there is the occurrence of ascites and/or malabsorption.<sup>(3)</sup>

Oral PUVA therapy can result in general and cosmetic benefits in cutaneous mastocytosis, especially telangiectasia macularis eruptiva perstans. There are risks involved in this treatment including skin cancer if over 200 treatments are required. PUVA therapy is consequently usually reserved for severe unresponsive cases in adults, and is rarely used in children.<sup>(3)</sup>

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# Removable dirt and debris may be mistaken for true hyperpigmented skin lesions

Primary Author: Matthew T. Smetanick, Corresponding Author: Scott J.M. Lim, D.O.

Concentrated build-up of dirt and debris on certain anatomical areas may sometimes mimic pigmented lesions such as melanocytic nevi and acanthosis nigricans. Patients will sometimes present with concern over the development of these pigmented 'lesions.' By recognizing such phenomena and using a simple

alcohol prep, the clinician may easily wipe away these 'lesions,' alleviating the patient's fears and avoiding unnecessary treatments and even surgical excisions.

We present a case of a 15 year-old white male who was referred to the dermatology clinic for evaluation of recurrent "moles" on the left side of his neck. The patient initially presented to his family physician almost two years prior with concern that these hyperpigmented lesions were cancerous. The patient was assured that the lesions were clinically benign junctional nevi. At the patient's request, the lesions were removed via shave excision without biopsy confirmation of the diagnosis. The lesions later returned in the same general location. The patient denied any irritation, pruritus, or bleeding related to the lesions.

On dermatologic exam, three distinct ovoid, hyperpigmented patches were observed measuring approximately 1x1 cm<sup>2</sup> on the left side of his neck, appear-

ing to be concentrated areas of dirt and debris (Figure 1). The dermatologic exam was also remarkable for cutaneous thickening and hyperpigmentation in the axillary and posterior cervical regions, characteristic of acanthosis nigricans. Based on previous clinical experiences involving grime-based lesions, the marks were removed by rubbing them with an alcohol prep (Figures 2-3). The patient was reassured that the lesions were neither benign nor dysplastic nevi. He was subsequently counseled on the need for better hygiene to prevent such lesions and recurrences. In addition, the patient was counseled on the potential significance of acanthosis nigricans and was advised to follow up with his family physician for appropriate monitoring and testing for diabetes and other endocrine disorders.

Additionally, we present a case of an 8 year-old white male, seen in consultation for evaluation of a "rash" involving the



**Figure 1.** Hyperpigmented patch on left side of neck. The other two 'lesions' have already been wiped away. Acanthosis nigricans is evident in posterior cervical region.



**Figure 2.** Left side of neck after wiping area with an alcohol prep. The dirt has not been completely removed from the patch seen in Figure 1.



**Figure 3.** Alcohol prep demonstrating removal of superficial dirt and debris from the hyperpigmented patch on left neck.



**Figure 4.** Hyperpigmented papules on anterior neck.



**Figure 5.** Hyperpigmented papules on left post-auricular region.



**Figure 6.** Removal of the lesions on anterior neck after wiping with an alcohol prep.



**Figure 7.** Removal of the lesions on left post-auricular region after wiping with an alcohol prep.

anterior neck and bilateral post-auricular regions, which had been present for six months. The patient was initially evaluated by his primary care physician, who clinically reached a diagnosis of acanthosis nigricans. Work-up was ordered, including a fasting glucose level that was normal. The "rash" was asymptomatic and characterized as speckled hyperpigmented papules, grouped into ovoid patches and oriented along the skin lines (Figures 4-5). The possibility of an accumulation of dirt and grime was considered. After wiping the lesions with an alcohol prep, the pigment was removed (Figures 6-7).

Prior to these cases, one author (S.J.M.L.) encountered a 50 year-old bald male who was concerned about a distinct

hyperpigmented plaque-like lesion on his scalp. Interestingly, the mark was wiped away with an alcohol prep, proving to be nothing more than a localized accumulation of dirt and sebaceous material. Such lesions can evidently develop in a progressive and chronic manner when not adequately scrubbed during bathing. Prolonged anxiety and/or treatment regimens can be avoided if one anticipates questionable lesions in body locations such as the scalp and body folds. The clinician can diagnose the problem and reassure the patient with a simple alcohol wipe.

Corresponding Author:  
Scott J.M. Lim, D.O.

Correspondence and reprint requests should be sent to:  
Scott J.M. Lim, D.O.  
5100 Peach Street, Erie, PA, 16509  
Office phone: 814-864-2625  
Fax: 814-868-9339  
E-mail: [slimderm@adelphia.net](mailto:slimderm@adelphia.net).

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# Erythema Nodosum Caused by Celebrex

Steven L.Harlan M.D., Mary Evers D.O.

## Abstract

We report a case of erythema nodosum caused by Celebrex (celecoxib). This adverse reaction has not been previously reported. A 63-year-old white female developed symptoms consistent with erythema nodosum. A thorough history, physical examination, laboratory evaluation, and radiologic studies failed to reveal another cause for erythema nodosum. Her symptoms resolved following cessation of Celebrex. We conclude that Celebrex should be added to the list of medications known to cause erythema nodosum.

Erythema nodosum is a hypersensitivity reaction that presents as a nodular erythematous eruption usually limited to the anterior and lateral aspects of the lower extremities. Other symptoms with erythema nodosum include low-grade fever, malaise, arthralgias, and lower extremity edema.<sup>1</sup> Many causes have been reported including infections, sarcoidosis, malignancies, Behcet's and Sweet's syndrome.<sup>2-4</sup> Medications that have been implicated include oral contraceptives, omeprazole, antibiotics, bromides, barbiturates, and sulfonamides.<sup>1,5,6</sup> We report a case of erythema nodosum caused by Celebrex (celecoxib), a cyclooxygenase-2 (COX-2) inhibitor. This side effect of Celebrex has never been reported.

## Case Report

A 63-year-old white female with a 20-year history of osteoarthritis was treated with multiple trials of nonsteroidals, which resulted in GI upset. She was placed on Celebrex 200mg po QD with a resolution of symptoms. Other medications taken simultaneously were Cholestyramine, Prempro, Pepcid, Lipitor, Zolof, and Accupril. She is not allergic to sulfonamides.

Approximately 2 months after initiation of Celebrex, the patient presented with right lower leg patchy erythema, pedal edema, and slight pruritis. In addition, there was some purplish discoloration combined with the edema suggestive of Henoch-Schonlein purpura. TSH, ANA, and Rheumatoid Factor were negative. Over the next two days the erythema and edema worsened and the left leg became involved. Bilateral lower leg nodose lesions evolved on the extensor surfaces of her legs. Chest X-Ray, ASO titer, ACE titer, ANCA, and ESR were all negative. Punch biopsy from the left leg revealed a reactive epidermis with benign hyperkeratosis. A perivascular mixed lymphocytic and polymorphonuclear (PMN) light infiltrate was noted around the superficial dermal vessels. In the subcutaneous fat, a heavy granulomatous mixed infiltration of giant cells, monocytes, and PMN's with toxic fibrinoid changes to small veins was noted in a septal panniculitis pattern (Fig-

ure 1). These findings are consistent with erythema nodosum. All of her medications were stopped and Indocin 25 mg TID was initiated.

The patient responded to treatment and no new lesions were noted within a week. Both legs remained edematous with nodose lesions slowly resolving on the extensor surfaces. In addition, Lyme test, tuberculin skin test, and venous Doppler of her legs were negative. Over a period of 4-6 weeks the nodules and edema resolved. The patient was restarted on all prior medications with the exception of Celebrex. There was no relapse of the erythema nodosum.

## Discussion

There is a strong association between treatment with sulfonamides and erythema nodosum. Celebrex is a sulfonamide-containing 1,5-diarylpyrazole derivative that selectively inhibits COX-2. COX-2 is one of two isoforms of the rate limiting enzyme cyclooxygenase that synthesizes prostaglandins- mediators of inflammation, renal blood flow, and gastric "cytoprotection". By selectively inhibiting only COX-2 Celebrex has shown to possess anti-inflammatory activity with little or no gastric effects. Currently it is recommended for the treatment of rheumatoid and osteoarthritis.<sup>7</sup> Cutaneous reactions involving Celebrex that have been reported include erythematous rash, maculopapular rash, pruritis, urticaria, exfoliative dermatitis, Erythema multiforme and toxic epidermal necrolysis.<sup>8</sup> No report of erythema nodosum linked to Celebrex has ever been reported. We propose that the sulfonamide-containing moiety of Celebrex is responsible for the erythema nodosum.

## Conclusion

The patient's history, physical examination, laboratory examinations, and X-ray findings failed to reveal another cause for erythema nodosum. The results of the biopsy are characteristic for erythema nodosum. There was no relapse of the erythema nodosum following Celebrex withdrawal and reintroduction of all prior medications. We conclude that Celebrex

Figure 1A

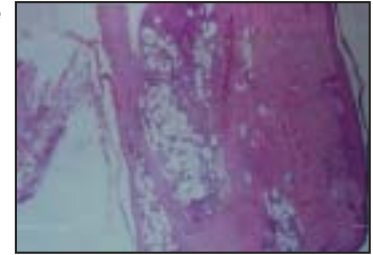


Figure 1B

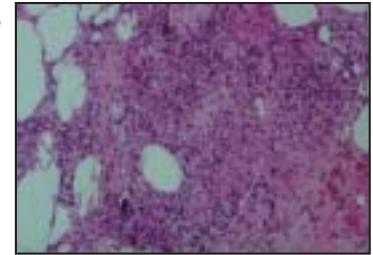


Figure 1 (A), Low and (B) high magnification views consistent with erythema nodosum. Note a heavy granulomatous mixed infiltration of giant cells, monocytes, and PMN's in a septal panniculitis pattern. (Hematoxylin-eosin stain; original magnifications: A, x40; B, x100.)

should be added to the drugs known to cause erythema nodosum.

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Corresponding Author: Steven L.Harlan M.D.  
Dermatology and Dermatologic Surgery Center PC  
8131 University Boulevard, Des Moines, Iowa 50325  
Adjunct Professor Des Moines University-Osteopathic Medical Center  
Phone: (515) 225-8180, Fax: (515) 225-2041  
E-mail: HARLAN8131@aol.com

# Treatment of Granuloma Annulare with Topical Tacrolimus 0.1% Ointment: A Phase IV Clinical Trial

Paul M. Bedocs, D.O., Thomas Fleming, M.D., Mandi R. Motter, R.N.

## Abstract

*Granuloma annulare (GA) is a common idiopathic granulomatous condition that responds poorly to many treatments. Our objective was to study the effects of topically applied tacrolimus 0.1% ointment on ten patients with GA. In an open label clinical trial, 10 female patients applied tacrolimus 0.1% ointment two times daily to the affected areas. The frequency of application was increased to three times daily for slow responders.*

*Results demonstrated that in this subset of patients with localized GA, tacrolimus ointment effectively reduced the size and symptoms of the lesions in all 8 patients who completed the study. Transient localized irritation occurred in 9 patients. Topical tacrolimus 0.1% ointment appears to be safe and effective in a subset of patients with localized GA. A larger study is needed to determine with greater confidence the percentage of patients likely to respond.*

## Introduction:

Granuloma annulare (GA) is a benign, idiopathic, granulomatous dermatosis of the integument that is recalcitrant to many treatments. Clinically, GA may have one of several presentations but is most commonly characterized by asymptomatic, erythematous to violaceous, smooth, annular and arcuate plaques with accentuated, indurated borders. Plaques of GA typically affect dorsal surfaces of the extremities but may affect any area. GA develops slowly and may remain unchanged for months or years before disappearing spontaneously without scarring or other residua. The diagnosis of GA can usually be made clinically, however, a biopsy is occasionally used to confirm clinical suspicion. Histologic evaluation classically demonstrates degraded collagen fibrils and mucin infiltrates surrounded by palisading granulomatous inflammation in the dermis.

Tacrolimus ointment is a nonsteroidal topical macrolide immunomodulator produced by *Streptomyces tsukabanaensis*. It has been demonstrated that tacrolimus inhibits T-lymphocytes activation, leading to decreased production of IL2, IL3, IL4, IL5, GM-CSF, TNF- $\alpha$  and gamma-interferon, many of which are hypothesized to play a role in the pathogenesis of GA.<sup>1,2</sup> This study assessed the therapeutic effect of treating GA with topical 0.1% tacrolimus ointment.

## Patients and Methods:

The study was a phase IV, open label, single center, clinical trial to evaluate the efficacy and safety of topically applied tacrolimus 0.1% ointment in 10 evaluable adult patients with GA. The diagnosis of the patient's GA was made clinically. Biopsy was not taken due to reports in the literature of spontaneous involution of lesions after biopsy.

Subject eligibility was determined at the pre-study screening visit and upon

confirmation of a negative, in-house KOH test. All eligible subjects returned to the clinic following any applicable concomitant medication washout for the treatment initiation visit. Of the ten patients enrolled, all were women. The duration of the patients' diseases ranged from 2 months to 3 years. Baseline safety and severity data was collected and the subject was provided with the study medication and instructions for use. Subjects applied tacrolimus 0.1% ointment bid as a thin coat covering the affected areas for up to 24 weeks. Dosing schedules were increased to a tid application if a 50% or greater improvement was not appreciated at the week 4 visit.

The subjects were evaluated every 4 weeks in the clinic throughout the treatment period. Efficacy was assessed using a calculated score that combined multiple clinical parameters including: erythema, discoloration, induration, presence of papules or nodules, pruritus and annular configurations. The primary efficacy endpoint was the Physician's Global Evaluation of Clinical Response in the GA Treatment Regions at the Week 24/ End-of-Study visit.

## Results:

All 8 patients who completed the study demonstrated a decrease in disease severity. The efficacy of tacrolimus ointment was apparent in the 8 individuals after the first week of treatment, yet they continued to improve throughout the 24-week course. Six of the 10 subjects who applied tacrolimus ointment demonstrated 50% or greater clearing by the end-of-study visit (Figure 1). Of the remaining 4 subjects, 2 obtained 25% clearing and 2 showed no improvement. The 2 patients who did not improve did not complete the study.

Initially, mild localized irritation consisting of primarily erythema was experienced by 9 of the subjects. However,



**Figure 1A, pre-treatment: Distinct annular plaques of GA.**



**Figure 1B, post-treatment: Marked improvement after 24 weeks of treatment with tacrolimus.**

with continued use, irritation subsided and dosing was not interrupted. No other adverse effects were observed.

## Discussion:


Many speculative hypotheses have been rendered to explain the pathogenesis of GA.<sup>3</sup> The literature reports possible associations with diabetes mellitus, mycobacterial infections, trauma, viral infections, insect bites, UV exposure, HLA antigens, contact dermatitis, immune complex vasculitis and circulating immunocomplexes.<sup>4-12</sup> Recent data suggests a delayed-type IV hypersensitivity reaction as the pathogenesis of GA. This mechanism is supported by the regular presence of activated T-helper 1 (Th-1) lymphocytes in the GA lesions.<sup>13</sup>

Tacrolimus inhibits T-lymphocyte activation and may therefore impact the progression or facilitate the regression of GA lesions. Tacrolimus inhibits T-lymphocyte activation by first binding to the intracellular protein FKBP.<sup>1,14</sup> The complex of tacrolimus-FKBP-calcium-calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin is inhibited. This effect has been shown to prevent the dephosphorylation and subsequent translocation of nuclear factors of activated T-cells, a nuclear component thought to initiate gene transcription for the formation of pivotal lymphokines such as interleukin-2 and gamma-interferon. Tacrolimus also inhibits the transcription for genes that encode IL-3, IL-4, IL-5, GM-CSF and TNF- $\alpha$ , all of which are involved in the early stages of T-cell activation.<sup>1,2</sup> Given its mechanism of action, and the role of T-lymphocytes in the pathogenesis of GA, it is easy to hypothesize how tacrolimus may impact disease progression.

The lack of clear understanding of the pathogenesis and the unpredictable natural history of GA complicates the evaluation and treatment of this common skin disorder. The present study demonstrates that a subset of patients with GA responded positively to treatment with topical tacrolimus 0.1% ointment. A larger study is necessary to determine with better confidence the percentage of patients likely to respond.

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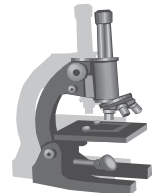


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\*ELIDEL is indicated for short-term and intermittent long-term therapy for *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, inadequate clinical response, or patient intolerance of such therapies.

ELIDEL is contraindicated in patients who are hypersensitive to pimecrolimus or any of the components of the cream. It should not be applied to areas of active cutaneous infections. Use should be carefully evaluated if varicella zoster virus, herpes simplex virus, or eczema herpeticum infections are present.

If patients have lymphadenopathy that is unresolved or of unclear etiology, discontinuation should be considered. Patients should minimize or avoid natural or artificial sunlight exposure. **ELIDEL should not be used with occlusive dressings.**

The most common adverse events seen in clinical studies included application-site burning, headache, pharyngitis, nasopharyngitis, cough, influenza, pyrexia, and viral infection.

In clinical studies, skin papilloma or warts were observed in 1% of ELIDEL patients.

The efficacy and safety of ELIDEL have not been studied beyond 1 year.

\*\*Intermittent therapy with ELIDEL has been studied up to 1 year. Treatment should be discontinued upon resolution of disease. Patients should be re-evaluated if symptoms persist beyond 6 weeks.

\*\*Data from moderate patients in a 6-month study conducted in adults to determine the safety and efficacy of ELIDEL in the long-term management of atopic dermatitis (N=192).

Reference: 1. Data on file, Novartis Pharmaceuticals Corporation.

Please see brief summary of Prescribing Information.

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**ELIDEL<sup>®</sup>**  
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# Elidel® (pimecrolimus) Cream 1%

FOR DERMATOLOGIC USE ONLY  
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## Rx only

**BRIEF SUMMARY:** Please see package insert for full prescribing information.

**INDICATIONS AND USAGE:** Elidel® (pimecrolimus) Cream 1% is indicated for short-term and intermittent long-term therapy in the treatment of *mild to moderate* atopic dermatitis in non-immunocompromised patients 2 years of age and older, in whom the use of alternative, conventional therapies is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies (see **DOSAGE AND ADMINISTRATION** in the full prescribing information).

**CONTRAINDICATIONS:** Elidel® (pimecrolimus) Cream 1% is contraindicated in individuals with a history of hypersensitivity to pimecrolimus or any of the components of the cream.

**PRECAUTIONS: General:** Elidel® (pimecrolimus) Cream 1% should not be applied to areas of active cutaneous viral infections. Studies have not evaluated the safety and efficacy of Elidel Cream in the treatment of clinically infected atopic dermatitis. Before commencing treatment with Elidel Cream, clinical infections at treatment sites should be cleared. While patients with atopic dermatitis are predisposed to superficial skin infections including eczema herpeticum (Kaposi's varicelliform eruption), treatment with Elidel Cream may be associated with an increased risk of varicella zoster virus infection (chicken pox or shingles), herpes simplex virus infection, or eczema herpeticum. In the presence of these skin infections, the balance of risks and benefits associated with Elidel Cream use should be evaluated. In clinical studies, 14 cases of lymphadenopathy (0.9%) were reported while using Elidel Cream. These cases of lymphadenopathy were usually related to infections and noted to resolve upon appropriate antibiotic therapy. Of these 14 cases, the majority had either a clear etiology or were known to resolve. Patients who receive Elidel Cream and who develop lymphadenopathy should have the etiology of their lymphadenopathy investigated. In the absence of a clear etiology for the lymphadenopathy, or in the presence of acute infectious mononucleosis, discontinuation of Elidel Cream should be considered. Patients who develop lymphadenopathy should be monitored to ensure that the lymphadenopathy resolves. In clinical studies, 15 cases of skin papilloma or warts (1%) were observed in patients using Elidel Cream. The youngest patient was age 2 and the oldest was age 12. In cases where there is worsening of skin papillomas or they do not respond to conventional therapy, discontinuation of Elidel Cream should be considered until complete resolution of the warts is achieved. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Despite the absence of observed phototoxicity in humans (see **ADVERSE REACTIONS**), Elidel Cream shortened the time to skin tumor formation in an animal photo-carcinogenicity study (see **Carcinogenesis, Mutagenesis, Impairment of Fertility**). Therefore, it is prudent for patients to minimize or avoid natural or artificial sunlight exposure. The use of Elidel Cream in patients with Netherton's Syndrome is not recommended due to the potential for increased systemic absorption of pimecrolimus. There are no data to support use of Elidel in immunocompromised patients. The use of Elidel Cream may cause local symptoms such as skin burning. Localized symptoms are most common during the first few days of Elidel Cream application and typically improve as the lesions of atopic dermatitis resolve. Most application site reactions lasted no more than 5 days, were mild to moderate in severity, and started within 1-5 days of treatment. (See **ADVERSE REACTIONS**.)

**Information for Patients:** Patients using Elidel should receive the following information and instructions:

- Patients should use Elidel Cream as directed by the physician. Elidel Cream is for external use on the skin only. As with any topical medication, patients or caregivers should wash hands after application if hands are not an area for treatment.
- Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVAB treatment) while using Elidel Cream.
- Patients should not use this medication for any disorder other than that for which it was prescribed.
- Patients should report any signs or symptoms of adverse reactions to their physician.
- Therapy should be discontinued after signs and symptoms of atopic dermatitis have resolved. Treatment with Elidel should be resumed at the first signs or symptoms of recurrence.
- Use of Elidel may cause reactions at the site of application such as a mild to moderate feeling of warmth and/or sensation of burning. Patients should see a physician if an application site reaction is severe or persists for more than 1 week.
- The patient should contact the physician if no improvement in the atopic dermatitis is seen following 6 weeks of treatment, or if at any time the condition worsens.

**Drug Interactions:** Potential interactions between Elidel and other drugs, including immunizations, have not been systematically evaluated. Due to the very low blood levels of pimecrolimus detected in some patients after topical application, systemic drug interactions are not expected, but cannot be ruled out. The concomitant administration of known CYP3A family of inhibitors in patients with widespread and/or erythrodermic disease should be done with caution. Some examples of such drugs are erythromycin, itraconazole, ketoconazole, fluconazole, calcium channel blockers and cimetidine.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A battery of *in vitro* genotoxicity tests, including Ames assay, mouse lymphoma L5178Y assay, and chromosome aberration test in V79 Chinese hamster cells and an *in vivo* mouse micronucleus test revealed no evidence for a mutagenic or clastogenic potential for the drug. No effect on fertility in female rats was noted at 10 mg/kg/day (12X MRHD based on AUC comparisons). No effect on fertility in male rats was noted at 45 mg/kg/day (23X MRHD based on AUC comparisons), which was the highest dose tested in this study.

**Pregnancy: Teratogenic Effects: Pregnancy Category C:** There are no adequate and well-controlled studies of topically administered pimecrolimus in pregnant women. The experience with Elidel Cream when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy. Pimecrolimus was transferred across the placenta in oral rat and rabbit embryofetal developmental studies. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from pimecrolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Elidel Cream may be used in pediatric patients 2 years of age and older. Three Phase 3 pediatric studies were conducted involving 1114 patients 2-17 years of age. Two studies were 6-week randomized vehicle-controlled studies with a 20-week open-label phase and one was a vehicle-controlled long-term (up to 1 year) safety study with the option for sequential topical corticosteroid use. Of these patients 542 (49%) were 2-6 years of age. In the short-term studies, 11% of Elidel patients did not complete these studies and 1.5% of Elidel patients discontinued due to adverse events. In the one-year study, 32% of Elidel patients did not complete this study and 3% of Elidel patients discontinued due to adverse events. Most discontinuations were due to unsatisfactory therapeutic effect. The most common local adverse event in the short-term studies of Elidel Cream in pediatric patients ages 2-17 was application site burning (10% vs. 13% vehicle); the incidence in the long-term study was 9% Elidel vs. 7% vehicle (see **ADVERSE REACTIONS**). Adverse events that were more frequent (>5%) in patients treated with Elidel Cream compared to vehicle were headache (14% vs. 9%) in the short-term trial. Nasopharyngitis (26% vs. 21%), influenza (13% vs. 4%), pharyngitis (8% vs. 3%), viral infection (7% vs. 1%), pyrexia (13% vs. 5%), cough (16% vs. 11%), and headache (25% vs. 16%) were increased over vehicle in the 1-year safety study (see **ADVERSE REACTIONS**). In 843 patients ages 2-17 years treated with Elidel Cream, 9 (0.8%) developed eczema herpeticum (5 on Elidel Cream alone and 4 on Elidel Cream used in sequence with corticosteroids). In 211 patients on vehicle alone, there were no cases of eczema herpeticum. The majority of adverse events were mild to moderate in severity. Elidel Cream is not recommended for use in pediatric patients below the age of 2 years. Two Phase 3 studies were conducted involving 436 infants age 3 months - 23 months. One 6-week randomized vehicle-controlled study with a 20-week open-label phase and one long term safety study were conducted. In the 6-week study, 11% of Elidel and 48% of vehicle patients did not complete this study; no patient in either group discontinued due to adverse events. Infants on Elidel Cream had an increased incidence of some adverse events compared to vehicle. In the 6-week vehicle-controlled study these adverse events included pyrexia (32% vs. 13% vehicle), URI (24% vs. 14%), nasopharyngitis (15% vs. 8%), gastroenteritis (7% vs. 3%), otitis media (4% vs. 0%), and diarrhea (8% vs. 0%). In the open-label phase of the study, for infants who switched to Elidel Cream from vehicle, the incidence of the above-cited adverse events approached or equaled the incidence of those patients who remained on Elidel Cream. In the 6 month safety data, 16% of Elidel and 35% of vehicle patients discontinued early and 1.5% of Elidel and 0% of vehicle patients discontinued due to adverse events. Infants on Elidel Cream had a greater incidence of some adverse events as compared to vehicle. These included pyrexia (30% vs. 20%), URI (21% vs. 17%), cough (15% vs. 9%), hypersensitivity (8% vs. 2%), teething (27% vs. 22%), vomiting (9% vs. 4%), rhinitis (13% vs. 9%), viral rash (4% vs. 0%), rhinorrhea (4% vs. 0%), and wheezing (4% vs. 0%). The effects of Elidel Cream on the developing immune system in infants are unknown.

**Geriatric Use:** Nine (9) patients ≥ 65 years old received Elidel Cream in Phase 3 studies. Clinical studies of Elidel did not include sufficient numbers of patients aged 65 and over to assess efficacy and safety.

**ADVERSE REACTIONS:** In human dermal safety studies, Elidel® (pimecrolimus) Cream 1% did not induce contact sensitization, phototoxicity, or photoallergy, nor did it show any cumulative irritation. In a one-year safety study in pediatric patients age 2-17 years old involving sequential use of Elidel Cream and a topical corticosteroid, 43% of Elidel patients and 68% of vehicle patients used corticosteroids during the study. Corticosteroids were used for more than 7 days by 34% of Elidel patients and 54% of vehicle patients. An increased incidence of impetigo, skin infection, superinfection (infected atopic dermatitis), rhinitis, and urticaria were found in the patients that had used Elidel Cream and topical corticosteroid sequentially as compared to Elidel Cream alone. In 3 randomized, double-blind vehicle-controlled pediatric studies and one active-controlled adult study, 843 and 328 patients respectively, were treated with Elidel Cream. In these clinical trials, 48 (4%) of the 1171 Elidel patients and 13 (3%) of 408 vehicle-treated patients discontinued therapy due to adverse events. Discontinuations for AEs were primarily due to application site reactions, and cutaneous infections. The most common application site reaction was application site burning, which occurred in 8%-26% of patients treated with Elidel Cream. The following

table depicts the incidence of adverse events pooled across the 2 identically designed 6-week studies with their open label extensions and the 1-year safety study for pediatric patients ages 2-17. Data from the adult active-controlled study is also included in this table. Adverse events are listed regardless of relationship to study drug.

	Treatment Emergent Adverse Events (>1%) in Elidel® Treatment Groups						
	Pediatric Patients* Vehicle-Controlled (6 weeks)		Pediatric Patients* Open-Label (20 weeks)		Pediatric Patients* Vehicle-Controlled (1 year)		Adult Active Comparator (1 year)
	Elidel® Cream (N=267) N (%)	Vehicle (N=136) N (%)	Elidel® Cream (N=335) N (%)	Elidel® Cream (N=272) N (%)	Vehicle (N=75) N (%)	Elidel® Cream (N=328) N (%)	
At least 1 AE	182 (68.2%)	97 (71.3%)	240 (72.0%)	230 (84.6%)	56 (74.7%)	256 (78.0%)	
<b>Infections and Infestations</b>							
<b>Upper Respiratory</b>							
Tract Infection NOS	18 (14.2%)	18 (13.2%)	65 (19.4%)	13 (4.8%)	6 (8.0%)	14 (4.3%)	
Nasopharyngitis	27 (10.1%)	10 (7.4%)	32 (9.6%)	72 (26.5%)	16 (21.3%)	25 (7.6%)	
Skin Infection NOS	8 (3.0%)	9 (5.1%)	18 (5.4%)	6 (2.2%)	3 (4.0%)	21 (6.4%)	
Influenza	8 (3.0%)	1 (0.7%)	22 (6.6%)	36 (13.2%)	3 (4.0%)	32 (9.8%)	
Ear Infection NOS	6 (2.2%)	2 (1.5%)	19 (5.7%)	9 (3.3%)	1 (1.3%)	2 (0.6%)	
Otitis Media	6 (2.2%)	1 (0.7%)	10 (3.0%)	8 (2.9%)	4 (5.3%)	2 (0.6%)	
Impetigo	5 (1.9%)	3 (2.2%)	12 (3.6%)	11 (4.0%)	4 (5.3%)	8 (2.4%)	
Bacterial Infection	4 (1.5%)	3 (2.2%)	4 (1.2%)	3 (1.1%)	0	6 (1.8%)	
Folliculitis	3 (1.1%)	1 (0.7%)	3 (0.9%)	6 (2.2%)	3 (4.0%)	20 (6.1%)	
Sinusitis	3 (1.1%)	1 (0.7%)	11 (3.3%)	6 (2.2%)	1 (1.3%)	2 (0.6%)	
Pneumonia NOS	3 (1.1%)	1 (0.7%)	5 (1.5%)	0	1 (1.3%)	1 (0.3%)	
Pharyngitis NOS	2 (0.7%)	2 (1.5%)	3 (0.9%)	22 (8.1%)	2 (2.7%)	3 (0.9%)	
Pharyngitis Streptococcal	2 (0.7%)	2 (1.5%)	10 (3.0%)	0	<1%	0	
Molluscum Contagiosum	2 (0.7%)	0	4 (1.2%)	5 (1.8%)	0	0	
Staphylococcal Infection	1 (0.4%)	5 (3.7%)	7 (2.1%)	0	<1%	3 (0.9%)	
Bronchitis NOS	1 (0.4%)	3 (2.2%)	4 (1.2%)	29 (10.7%)	6 (8.0%)	8 (2.4%)	
Herpes Simplex	1 (0.4%)	0	4 (1.2%)	9 (3.3%)	2 (2.7%)	13 (4.0%)	
Tonsillitis NOS	1 (0.4%)	0	3 (0.9%)	17 (6.3%)	0	2 (0.6%)	
Viral Infection NOS	2 (0.7%)	1 (0.7%)	1 (0.3%)	18 (6.6%)	1 (1.3%)	0	
Gastroenteritis NOS	0	3 (2.2%)	2 (0.6%)	20 (7.4%)	2 (2.7%)	6 (1.8%)	
Chickenpox	2 (0.7%)	0	3 (0.9%)	8 (2.9%)	3 (4.0%)	1 (0.3%)	
Skin Papilloma	1 (0.4%)	0	2 (0.6%)	9 (3.3%)	<1%	0	
Tonsillitis Acute NOS	0	0	0	7 (2.6%)	0	0	
<b>Upper Respiratory Tract</b>							
Infection Viral NOS	1 (0.4%)	0	3 (0.9%)	4 (1.5%)	0	1 (0.3%)	
Herpes Simplex Dermatitis	0	0	1 (0.3%)	4 (1.5%)	0	2 (0.6%)	
Bronchitis Acute NOS	0	0	0	4 (1.5%)	0	0	
Eye Infection NOS	0	0	0	3 (1.1%)	<1%	1 (0.3%)	
<b>General Disorders and Administration Site Conditions</b>							
Application Site Burning	28 (10.4%)	17 (12.5%)	5 (1.5%)	23 (8.5%)	5 (6.7%)	85 (25.9%)	
Pyrexia	20 (7.5%)	12 (8.8%)	41 (12.2%)	34 (12.5%)	4 (5.3%)	4 (1.2%)	
<b>Application Site</b>							
Reaction NOS	8 (3.0%)	7 (5.1%)	7 (2.1%)	9 (3.3%)	2 (2.7%)	48 (14.6%)	
Application Site Irritation	8 (3.0%)	8 (5.9%)	3 (0.9%)	1 (0.4%)	3 (4.0%)	21 (6.4%)	
Influenza Like Illness	1 (0.4%)	0	2 (0.6%)	5 (1.8%)	2 (2.7%)	6 (1.8%)	
Application Site Erythema	1 (0.4%)	0	0	6 (2.2%)	0	7 (2.1%)	
Application Site Pruritus	3 (1.1%)	2 (1.5%)	2 (0.6%)	5 (1.8%)	0	16 (5.5%)	
<b>Respiratory, Thoracic and Mediastinal Disorders</b>							
Cough	31 (11.6%)	11 (8.1%)	31 (9.3%)	43 (15.8%)	8 (10.7%)	8 (2.4%)	
Nasal Congestion	7 (2.6%)	2 (1.5%)	6 (1.8%)	4 (1.5%)	1 (1.3%)	2 (0.6%)	
Rhinorrhea	5 (1.9%)	1 (0.7%)	3 (0.9%)	1 (0.4%)	1 (1.3%)	0	
Asthma Aggravated	4 (1.5%)	3 (2.2%)	13 (3.9%)	3 (1.1%)	1 (1.3%)	0	
Sinus Congestion	3 (1.1%)	1 (0.7%)	2 (0.6%)	<1%	<1%	3 (0.9%)	
Rhinitis	1 (0.4%)	0	5 (1.5%)	12 (4.4%)	5 (6.7%)	7 (2.1%)	
Wheezing	1 (0.4%)	1 (0.7%)	4 (1.2%)	2 (0.7%)	<1%	0	
Asthma NOS	2 (0.7%)	1 (0.7%)	11 (3.3%)	10 (3.7%)	2 (2.7%)	8 (2.4%)	
Epistaxis	0	1 (0.7%)	0	9 (3.3%)	1 (1.3%)	1 (0.3%)	
Dyspnea NOS	0	0	0	5 (1.8%)	1 (1.3%)	2 (0.6%)	
<b>Gastrointestinal Disorders</b>							
Abdominal Pain Upper	11 (4.1%)	6 (4.4%)	10 (3.0%)	15 (5.5%)	5 (6.7%)	1 (0.3%)	
Sore Throat	9 (3.4%)	5 (3.7%)	15 (4.4%)	22 (8.1%)	4 (5.3%)	12 (3.7%)	
Vomiting NOS	8 (3.0%)	6 (4.4%)	14 (4.2%)	18 (6.6%)	6 (8.0%)	2 (0.6%)	
Diarrhea NOS	3 (1.1%)	1 (0.7%)	2 (0.6%)	21 (7.7%)	4 (5.3%)	7 (2.1%)	
Nausea	1 (0.4%)	3 (2.2%)	4 (1.2%)	11 (4.0%)	5 (6.7%)	6 (1.8%)	
Abdominal Pain NOS	1 (0.4%)	1 (0.7%)	5 (1.5%)	12 (4.4%)	3 (4.0%)	1 (0.3%)	
Toothache	1 (0.4%)	1 (0.7%)	2 (0.6%)	7 (2.6%)	1 (1.3%)	2 (0.6%)	
Constipation	1 (0.4%)	0	2 (0.6%)	10 (3.7%)	<1%	0	
Loose Stools	0	1 (0.7%)	4 (1.2%)	<1%	<1%	0	
<b>Reproductive System and Breast Disorders</b>							
Dysmenorrhea	3 (1.1%)	0	5 (1.5%)	3 (1.1%)	1 (1.3%)	4 (1.2%)	
<b>Eye Disorders</b>							
Conjunctivitis NEC	2 (0.7%)	1 (0.7%)	7 (2.1%)	6 (2.2%)	3 (4.0%)	10 (3.0%)	
<b>Skin &amp; Subcutaneous Tissue Disorders</b>							
Urticaria	3 (1.1%)	0	1 (0.3%)	1 (0.4%)	<1%	3 (0.9%)	
Acne NOS	0	1 (0.7%)	1 (0.3%)	4 (1.5%)	<1%	6 (1.8%)	
<b>Immune System Disorders</b>							
Hypersensitivity NOS	11 (4.1%)	6 (4.4%)	16 (4.8%)	14 (5.1%)	1 (1.3%)	11 (3.4%)	
<b>Injury and Poisoning</b>							
Accident NOS	3 (1.1%)	1 (0.7%)	1 (0.3%)	<1%	1 (1.3%)	0	
Laceration	2 (0.7%)	1 (0.7%)	5 (1.5%)	<1%	<1%	0	
<b>Musculoskeletal, Connective Tissue and Bone Disorders</b>							
Back Pain	1 (0.4%)	2 (1.5%)	1 (0.3%)	<1%	0	6 (1.8%)	
Arthralgias	0	0	1 (0.3%)	3 (1.1%)	1 (1.3%)	5 (1.5%)	
<b>Ear and Labyrinth Disorders</b>							
Earache	2 (0.7%)	1 (0.7%)	0	8 (2.9%)	2 (2.7%)	0	
<b>Nervous System Disorders</b>							
Headache	37 (13.9%)	12 (8.8%)	38 (11.3%)	69 (25.4%)	12 (16.0%)	23 (7.0%)	

\*Ages 2-17 years

**DOSAGE AND ADMINISTRATION:** Apply a thin layer of Elidel® (pimecrolimus) Cream 1% to the affected skin twice daily and rub in gently and completely. Elidel may be used on all skin surfaces, including the head, neck, and intertriginous areas. Elidel should be used twice daily for as long as signs and symptoms persist. Treatment should be discontinued if resolution of disease occurs. If symptoms persist beyond 6 weeks, the patient should be re-evaluated. The safety of Elidel Cream under occlusion, which may promote systemic exposure, has not been evaluated. **Elidel Cream should not be used with occlusive dressings.**

Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F). Do not freeze.

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# Hailey-Hailey The Great Imitator

Robert A. Norman, DO, MPH, Joshua Dawalt, DO

## Abstract

*Hailey Hailey Disease, also known as Benign Familial Pemphigus, is a chronic, recurrent, autosomal dominant, blistering disease that may significantly affect quality of life<sup>(1)</sup>.*

A 47 y/o female with a thirteen year of disease “everywhere there is a crease” reported her disease started with a sore red rash under her armpits, under her breasts and around her groin and buttocks. When she is placed in a stressful situation or in humid, moist conditions she flares up with seeping crusted erosions causing her great discomfort and embarrassment. She also complains of premenstrual exacerbation. Her past medical history was significant for asthma, bronchitis and kidney stones. Her family history was negative for heart disease, diabetes, and skin cancer. She had a positive history for Hailey-Hailey on the paternal side of family (father and cousins). Her past treatment included ciprofloxin, triamcinolone acetonide, ketoconazole, ketoconazole shampoo, cyclosporine (oral solution topically once daily), white vinegar, fluconazole, and laser therapy. She states only diphenhydramine 50 mg three times per day and ciprofloxin help.

Hailey Hailey Disease (H-H Dz) is not easily recognized, and in many cases is mistaken for something else. Because of the body regions where it is usually found, high friction areas such as armpits, under breasts, genitals, and inner thighs, it is commonly first mistaken for bacterial infection, chronic fungal infections, or in severe cases other bullous disorders like Pemphigus Vulgaris.<sup>(2,3)</sup> An antimicrobial agent or topical corticosteroid (both of which are often used) will many times calm down a flare up. But, if a correct diagnosis is not made and exacerbating factors are not recognized, recurrences occur. Therefore, it becomes extremely important for the physician to at least recognize the existence of this disorder in his or her own differential diagnosis. Once this has been done, the family physician will become a vital participant in helping to manage and control the disease, largely increasing the quality of life of each of these patients.

Certainly, H-H Dz is not a common disorder, affecting only one person in a million. But because this is an autosomal dominant disease, when it does affect the person it affects the entire family, often showing up inter-generationally, including siblings and extended family members. Due to the autosomal dominance, each

child of an afflicted individual has a fifty percent chance of obtaining the disorder, and both sexes are affected equally with some evidence that there is partial penetration of the genetic disorder<sup>(3,4)</sup>.

In trying to understand the genetic defect that causes H-H Dz, it is important to review the physiology of skin structure. There are three main layers of the skin. The three layers include the epidermis, which is the outermost layer; the dermis, which is the middle layer; and the subcutaneous layer, which is the bottom layer. The epidermis is made up of primarily keratinocytes, or epidermal cells, and is divided into four layers. From bottom to top, it includes the basal cell layer (stratum basalis); the spiny cell layer (stratum spinosum); the granular layer (stratum granulosum); and finally on the surface sits the cornified layer (stratum corneum). Lying below the stratum basalis and above the dermis layer sits the basement membrane with the extremely important function of maintaining strength and structure to the skin, by attaching the basal cell layer to the dermis. Maintaining strength and structure is also performed by small attachments between the keratinocytes called desmosomal complexes. These complexes consist of the desmosome and the tonofilaments, both of which function to hold the keratinocytes together<sup>(5)</sup>. It is in these desmosomal complexes that the genetic defect of H-H Dz produces its affect<sup>(4,6)</sup>.

Unlike the Pemphigus disorders, for which H-H Dz is also often mistaken, the defect to the desmosomal proteins is not due to autoantibodies, but instead because of genetic wiring which helps in forming these proteins<sup>(7)</sup>. It is this defect that is responsible for causing loss of cellular attachment among the keratinocytes and, thus, skin breakdown and bullous formation similar to Pemphigus. The mutation is found in a gene on chromosome 3, and interestingly, researchers have recently found that this gene is responsible for making a calcium pump. It is thought that the calcium inside the cell signals the desmosomal complexes, or “sticky junctions”; to tell exactly how “sticky” they need to be. So in H-H Dz, where the pumps in many of the skin cells do not work, faulty signals are sent which decrease the cells’ ability to hold together,



Figure 1



Figure 2



Figure 3

called acantholysis.<sup>(6)</sup> The skin breaks and becomes raw, forms blisters, allows for ripe conditions of overlying infection, and presents as H-H Dz.

So, how does H-H Dz present, and how would a family doctor be able to recognize and treat the disorder? Usually, patients will present in the third or fourth decade with erythematous, localized patches or plaques of minute vesicles or bullae with crusted erosions especially in areas of moisture and friction such as the

axilla, groin, or under breasts<sup>(2,8)</sup>. Burning, pain and itching accompany the eruptions, and a malodorous seeping clear or pus-like fluid is many times present especially in a flare up. In some patients, longitudinal white bands are found on the fingernails, and unlike other familial bullous disorders, mucosal involvement is very rare<sup>(2,4,9)</sup>.

It usually starts out mild, and increases in severity as time passes, reaching a peak in the so-called flare-ups, thought by most to be a result of an overlying infection, which is either bacterial or fungal<sup>(4)</sup>. One of its other distinguishing characteristics is its recurrent nature. For much of the time it is either not present or mild, not causing the patient much discomfort; but, when external factors occur, such as seasonal changes, stress, or restrictive clothing, the flare that then occurs can be debilitating. The areas affected are in highly frictional regions of the body, and with the body in constant movement; these regions are especially emphasized which in turn elicits pain. Finally, with the seeping of malodorous fluid occurring, great embarrassment afflicts many of these patients, which can significantly affect them socially<sup>(2,4,8)</sup>. If a suspicion is established with a family history, a biopsy is standard for making the diagnosis.

As if recognizing the disorder is not difficult enough, finding the right treatment can be as strenuous. There is no one specific method or modality in doing so, and unfortunately, refractory cases occur, making it even more frustrating. But on the other hand, many cases are manageable on an outpatient basis, making the primary care physician a vital aspect to their management. Discussions with H-H Dz patients show that it is important to find the regime that works best for each patient<sup>(10)</sup>. To help in making this easier, it is useful to break down each case into maintenance therapy, therapy for flare-ups, and refractory therapy.

In maintenance therapy, improving overall quality of life and preventing flare-ups are the emphasis. First, and most important, a healthy weight, which will help in minimizing friction and moisture on certain regions of the body, should be emphasized. Instructing patients to use cool compresses and dressings, as well as keeping the body parts as dry as possible by using a hair dryer following a bath should also be stressed<sup>(7,10)</sup>. Simple preventive acts in general hygiene and toiletry can make a lot of difference, which includes certain bathing accessories. Many over-the-counter remedies including Tea-Tree Oil, Oilatum Plus, and oatmeal products such as Aveeno Colloidal Oatmeal have been recommended by H-H Dz sufferers as being especially

soothing and important in keeping the skin supple<sup>(10)</sup>.

It has also been recommended by other sufferers to use an astringent, a drying agent used in management of hyperhidrosis<sup>(4,10)</sup>. Again there are several over-the-counter choices, including Aluminum Chloride (Drysol) or Mitchum Clear Gel (that is sold as an antibacterial deodorant) that may be applied to affected regions each night for a week and then on a whenever needed basis works well. The latter uses a triple nozzle top and ejects the gel by a turn screw in the base, thus minimizing any possible cross infection from using a roll on top<sup>(10)</sup>. Finally, recognizing that an overlying bacterial or fungal infection is usually a cause of a flare up is important to all H-H Dz sufferers. If caught early enough, a flare-up can be prevented<sup>(2,4,8)</sup>.

Flare-ups are common to all H-H Dz sufferers, and instructing the patient to be aware of this becomes necessary<sup>(4)</sup>. When a flare up does occur, the physician should first question whether an external factor such as weather changes, stress, or restrictive clothing is the partial cause<sup>(2,4)</sup>. Working on changing or at least trying to avoid these factors can help tremendously, and might allow other treatments to be saved for later. Then, understanding that infection, maceration, and friction induce a cascade of inflammation responsible for the flare up is the next step<sup>(11)</sup>. It is in this understanding that physicians have found that these flare-ups often respond to antimicrobials and corticosteroids.

For some cases, a topical antibiotic cream such as clindamycin or erythromycin used twice a day will be a first and only line of treatment. Combining this with intermittent use of a mild to moderate topical corticosteroid, also twice a day, may be just what is needed. For some widespread flares a systemic antibiotic may be required. In this case erythromycin 500mg twice a day, clindamycin 300mg four times a day, or tetracycline 500mg four times a day are all options. A bacterial culture and sensitivity can then provide the much needed additional information for gearing further treatment, and in many cases a fungal swab may be needed to determine if there is also an overlying fungal infection which would then require an antifungal agent such as ketoconazole cream 2% applied once or twice a day for two to six weeks. Once the flare up is diminished with the above protocols, maintenance therapy with an oral antibiotic such as erythromycin 250mg once daily can be very beneficial in helping to prevent the next flare-up<sup>(1,2,4,8,10)</sup>.

In refractory cases, the aim is at stopping the inflammatory response of T lymphocytes and cytokine transcription, both of which have recently been found to be increased in severe H-H Dz. Such modalities able to do this include immunosuppressants, oral corticosteroids, and occasionally, a retinoid such as isotretinoin<sup>(2,4)</sup>. Among the immunomodulators shown to have a strong effect in refractory cases, topical Tacrolimus (FK506) 0.1% ointment applied twice daily has been shown to have significant reduction in the extent of disease with minimal discernible side effects<sup>(11)</sup>. Oral methotrexate 5mg once per week has also been shown to improve refractory cases, but, with hepatic and renal function being a concern in patients using this, it should only be used as one of the last resorts<sup>(10)</sup>.

Oral corticosteroids and isotretinoin use are also last resorts. With oral corticosteroids, rebound flare-ups are common once the medication is discontinued emphasizing that these should only be used in severe cases on a short-term basis<sup>(4)</sup>. With isotretinoin, used in this case for its ability to inhibit sebaceous gland function allowing for dryer skin, side effects such as liver toxicity and possible teratogenicity not to mention the cost of therapy also make it a last resort. Finally, other modalities such as carbon dioxide laser therapy, dermabrasion, PUVA, oral and topical cyclosporine, oophorectomy, and photodynamic therapy with topical 5-aminolevulinic acid with subsequent irradiation therapy have all been used in the most refractory cases. Definitive care has been shown by each of these, but with scarring to afflicted regions a potential risk, these are only reserved for the most unmanageable cases<sup>(1,4,8,12,13,14,15,16,17)</sup>.

As can be seen from above, the variety of treatments and modalities are vast. It is important from a patient's perspective to know both the type of treatment and the etiology of their problem. To those suffering from H-H Dz, it is imperative that physicians, including family doctors, be at least aware of its existence. For when the time comes that a patient with an odd rash, who has tried everything to make it better, comes to the office in much distress, and not aware of their family history, H-H Dz will be a possibility. Allowing for an earlier diagnosis results in an earlier treatment regime greatly improves the patient's quality of life, which is the goal of every physician.

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# Optimal Treatment of Onychomycosis: A Status Report on Oral Antifungal Therapy

Marcus Goodman, B.S., MS-IV, James Q. Del Rosso, D.O., FAOCD

The management of onychomycosis has been plagued with frustration for physicians and patients due to difficulty in achieving cure, especially with topical approaches. The availability of the "newer generation of oral agents" includes the triazoles (itraconazole, fluconazole) and terbinafine (an allylamine compound), proven to achieve higher cure rates than older oral antifungal agents (griseofulvin, ketoconazole) and topical therapies. The "newer generation agents" have significantly improved the treatment of onychomycosis due to higher cure rates; continued experience with the newer agents has provided additional support of their favorable safety profiles.<sup>1</sup>

The following updates information on (a) the use of oral antifungal agents for the treatment of onychomycosis (b) recommended monitoring guidelines and (c) safety profiles. The review emphasizes the "newer" oral agents approved by the Food and Drug Administration (FDA) for treatment of onychomycosis in the United States, itraconazole and terbinafine. As onychomycosis is rarely cleared utilizing topical agents or surgical approaches as monotherapy, appropriate utilization of oral antifungal therapy provides the greatest chance of achieving mycologic cure and improving the appearance of affected nails.

## Currently Available Oral Antifungal Agents

Although itraconazole, fluconazole and terbinafine are commonly referred to as "newer" oral antifungal agents, this categorization is based on the conspicuous absence of additional agents, especially for cutaneous indications, since 1996. With regard to treatment of onychomycosis and other cutaneous uses, itraconazole and terbinafine are "time tested" in terms of efficacy and safety, with a continuous accumulation of clinical experience in several million patients.

## Spectrum of Antimycotic Coverage for Onychomycosis

Dermatophytes. Over 90% of mycotic toenail infections are caused by dermatophytes, with *Trichophyton rubrum* reported to be the most common pathogen.<sup>1,2</sup> Both itraconazole and terbinafine exhibit activity against dermatophytes, based on *in vitro* studies and evaluations of clinical efficacy.<sup>1-4</sup> The majority of study data collected on treatment of onychomycosis relates to dermatophyte-induced disease.

Yeasts. In immunocompetent patients, *Candida* onychomycosis of toenails is less common than dermatophyte infection. *Candida* spp, especially *C. albicans*, are more likely to be a factor in fingernail infection, including immune competent patients, immunocompromised individuals, and patients with peripheral vascular

<b>Oral Drug</b>	<b>Initial Availability in US</b>	<b>FDA-Approved Indications (US Product Monographs)</b>
<b>Griseofulvin</b>	1958	- Dermatophyte infections of skin, hair, nails
<b>Ketoconazole</b>	1981	- Treatment of severe recalcitrant dermatophyte infections unresponsive to topical therapy or griseofulvin or in patients unable to take griseofulvin - Candidiasis including chronic mucocutaneous candidiasis and oral thrush - Several deep fungal mycoses
<b>Fluconazole</b>	1990	- Vaginal, oropharyngeal and esophageal candidiasis, cryptococcal meningitis
<b>Itraconazole</b>	1992	- Toenail and fingernail dermatophyte (capsules)* onychomycosis - Systemic mycoses inclusive of aspergillosis, histoplasmosis and blastomycosis
<b>Terbinafine</b>	1996	- Toenail and fingernail dermatophyte onychomycosis

(\*Oral solution of itraconazole available and approved for oropharyngeal and esophageal candidiasis and empiric therapy in febrile neutropenic patients with suspected fungal infection)

disease affecting the fingers, such as Raynaud's phenomenon.<sup>1,2</sup> Itraconazole is active against several *Candida* species including *C. albicans* and *C. parapsilosis*.<sup>2,4</sup> Terbinafine exhibits a greater degree of variability in its activity against pathogenic yeasts. *C. parapsilosis* has been reported to be responsive with lesser activity noted against *C. albicans*.<sup>3,5</sup>

Non-Dermatophyte Molds. Due to

lower prevalence among patients with onychomycosis, data on treatment of non-dermatophyte mold infection is more limited.<sup>6-8</sup> Itraconazole has demonstrated efficacy for nondermatophyte mold infections including *Aspergillus* spp, *Scopulariopsis brevicaulis* and *Fusarium* spp.<sup>7,8</sup> The latter organism tends to be the most refractory, with combination treatment using surgical debridement and topical therapy more likely to be effective.

Among the non-dermatophyte mold infections treated with itraconazole, infection with *Aspergillus spp* appears to be the most responsive.<sup>7</sup> In some cases of non-dermatophyte mold onychomycosis, longer durations of treatment than those typically required for dermatophyte onychomycosis may be needed to achieve clearance of infection and clinical improvement. Data on terbinafine use for non-dermatophyte onychomycosis is also limited to relatively small case collections and isolated reports. Terbinafine has been shown to be effective in some cases of *S. brevicaulis* nail infection; cure rates appear to be lower than with dermatophyte disease and a longer duration of therapy is required.<sup>3,5</sup> In some cases, however, itraconazole and terbinafine have demonstrated efficacy for onychomycosis caused by *S. brevicaulis* using the same regimens as those recommended for dermatophyte disease.<sup>8</sup>

Currently available oral antifungal agents exhibit little to no clinical efficacy for the treatment of onychomycosis caused by *Onychocola canadensis*, *Scytalidium hyalinum* and *Scytalidium dimidiatum*.<sup>2,9</sup>

## Reported Regimens and Responses in Dermatophyte Onychomycosis

A myriad of trials have been completed evaluating both itraconazole and terbinafine for the treatment of dermatophyte onychomycosis, especially toenail disease.<sup>3,5,10,11</sup> Both blinded and open-label trials have been completed using a variety of parameters to evaluate the success of treatment. Evaluation after nail plate outgrowth (12 months after start of therapy) has been commonly used as the study endpoint. Criteria evaluating disease clearance in "target nails" has typically included mycologic cure, defined as both a negative direct microscopy (potassium hydroxide preparation) and fungal culture, clinical cure, defined as a completely normally appearing nail, and clinical response (or success), usually defined as a combination of completely normal appearing nails and those that are markedly improved in visible appearance.

**Regimens.** For toenail onychomycosis in adults, terbinafine has primarily been evaluated using continuous therapy with 250 mg daily for a duration of 12 or 16 weeks.<sup>2,3,5,10</sup> At present, studies evaluating intermittent regimens with terbinafine are limited with regard to the number of patients treated.<sup>10</sup> Itraconazole has been evaluated in adult patients with toenail onychomycosis using either intermittent therapy with 200 mg twice daily for 1 week per month ("pulse" therapy) over 3

or 4 cycles or continuous therapy with 200 mg daily for 12 or 16 weeks.<sup>2,4,10,11</sup> As responses have suggested either greater or comparable efficacy with the intermittent approach, pulse therapy has become the more common prescribing practice when using itraconazole.<sup>10,12</sup> Both itraconazole and terbinafine are capable of achieving significantly higher cure rates with shorter treatment courses, as compared to griseofulvin and ketoconazole, due to their more favorable pharmacokinetics in the nail unit; persistent therapeutic drug levels are noted within the nail for several months after discontinuation of therapy and clearance from the systemic circulation (Figure 1).<sup>13</sup>

**Treatment Responses.** Complete discussions of available onychomycosis trials, comparative trials and reported cure rates are beyond the scope of this review. Although a range of cure rates have been published, available data from a variety of research sources clearly supports the need for oral antifungal therapy when the desired goal is to provide the best chance of clearing onychomycosis.<sup>1,2,10</sup> Overall meta-averages and pooled data for dermatophyte toenail onychomycosis with itraconazole pulse therapy report a clinical cure rate of 58 + 10%, a clinical response rate of 82 + 3%, and mycologic cure rate of 77 + 5%.<sup>10,12</sup> Similar meta-averages and pooled analysis with terbinafine report a clinical cure rate of 64 + 8%, a clinical response rate of 76 + 8% and a mycologic cure rate of 80 + 5%.<sup>3,10</sup>

## Adjunctive Treatments and Adjustments in Therapy

**Reasons For Treatment Failure.** Poor compliance and inadequately prescribed treatment are obvious causes of treatment failure. Less obvious causes associated with an increased risk of treatment failure with oral antifungal monotherapy relate to specific clinical presentations and physical factors. The use of adjunctive surgical debridement has been shown to enhance response to treatment, especially in cases of dermatophytomas and spikes, lateral columns of disease, extensive onycholysis and marked nail plate thickening.<sup>14</sup>

**Adjustments In Therapy.** The use of booster therapy has been advocated in patients demonstrating a slower than anticipated response.<sup>15</sup> Using nail marking (grooving) techniques to assess plate growth, if at least 4 mm of new clear proximal plate is not noted within 3 months of finishing the course of oral therapy, additional treatment is probably warranted (ie. additional pulse of itraconazole, additional month of terbinafine). If culture positivity for the same organism (dermatophyte) is documented at 6 months from baseline (3

months after completion of oral therapy), this suggests significant persistence of infection and has been correlated with a greater likelihood of treatment failure; an additional course of oral therapy is suggested.<sup>3,16</sup> An extension study with terbinafine has also confirmed the value of clinical examination at 18 months after baseline. Clearance at this point in time suggests a reasonable likelihood of more prolonged benefit; if disease persistence or "relapse" is noted at this point, an additional course of therapy is likely to induce a sustained response.<sup>16</sup>

**Prevention of Recurrence.** With regard to onychomycosis, definitions of relapse versus reinfection have not been well-defined and are arbitrary. The redevelopment of previously cleared onychomycosis may represent recurrence of the same infection or may be the result of a new infection related to recolonization of the foot with dermatophyte organisms. The longer the time period until the "new" infection develops, the greater is the assumption that reinfection with an independent organism has occurred. In any event, it is widely accepted that dermatophyte onychomycosis starts first as tinea pedis or pedal colonization, prior to migration into the nail bed and undersurface of the plate.<sup>2</sup>

In a study of patients with toenail onychomycosis who cleared with itraconazole or terbinafine, patients were followed every 3 months over a period of 3 years.<sup>17</sup> Relapse rates increased over time, reported as 8.3% at 1 year 19.4% at 2 years and 22.2 % at 3 years.

Considering the widespread presence of dermatophyte organisms in the environment, and the tendency for many individuals to harbor or become infected with dermatophytes (ie. *T. rubrum*) due to a genetic "immunologic blind spot", such rates of recurrent infection are not surprising. Although large scale studies are not available, initiation of topical antifungal therapy applied to pedal skin after completion of the course of oral antifungal treatment is suggested to suppress dermatophyte recolonization of the foot and reduce the risk of reinfection.<sup>2</sup>

## Safety Considerations

**Patient Populations.** Both agents have been utilized in elderly patients, in diabetic patients, and in immunocompromised patients with favorable efficacy and safety documented.<sup>2,10,18</sup>

Although data is more limited with regard to the number of children treated with onychomycosis, both itraconazole and terbinafine have been used effectively and safely in this population.<sup>19</sup> This is not surprising as both agents have

been reported to be effective and safe in several reports of children treated for tinea capitis.<sup>20</sup>

**Adverse Reactions.** After 11 years of itraconazole use and 7 years of terbinafine use in the United States, and several additional years of usage worldwide, the adverse reaction profiles of these agents are well established. The incidence of "nuisance" side effects such as transient skin eruptions, headache and gastrointestinal upset are low (<1 – 5%) with both agents. Asymptomatic and transient elevations of hepatic enzymes have also been observed (< 4%).<sup>2,3,10</sup> Terbinafine has been associated with reversible changes in taste in 0.4 % of patients, usually developing during the first few weeks treatment, and loss of taste in 0.3 % of patients, associated with a more delayed onset of 4 to 8 weeks.<sup>3,5,21</sup> Occasional cases of reversible cutaneous reactions have been reported including subacute cutaneous lupus with terbinafine and acute generalized exanthematous pustulosis with both itraconazole and terbinafine.<sup>22-24</sup>

Severe adverse reactions are rare with both itraconazole and terbinafine.<sup>2-5,10</sup>

Rare cases of symptomatic hepatotoxicity have been reported sporadically with both agents.<sup>10</sup> Sporadic reports of hematologic abnormalities have also been published in association with terbinafine use; the incidence of significant neutropenia is estimated to be 1 in 400,000 patients.<sup>3</sup> Caution regarding the potential for exacerbation of congestive heart failure by itraconazole has been reported based on adverse reaction reports; use of itraconazole for the treatment of onychomycosis is contraindicated in this patient population.<sup>25</sup> Overall, considering the large number of patients treated with both itraconazole and terbinafine, the safety profiles of both of these agents is very favorable. Most patients complete treatment without difficulty, with rational patient monitoring serving to detect the vast majority of rare adverse events.

**Drug Interactions.** Itraconazole, an inhibitor of cytochrome 3A4 (CYP 3A4), may be associated with potentially significant drug interactions with other drugs metabolized by this same enzyme.<sup>26</sup> Use of itraconazole is contraindicated with some hypnotic agents (triazolam, midazolam), some HMG-CoA reductase inhibitors (lovastatin, simvastatin, atorvastatin), cisapride, quinidine, dofetilide and pimozide.<sup>25</sup> Cautious co-administration or avoidance of concomitant use is suggested in patients treated with digoxin and some calcium channel blockers.<sup>25-27</sup> As with other azole antifungal agents, cautious use is also suggested in patients

treated with cyclosporin.<sup>26,28</sup> Itraconazole requires an environment of gastric acidity for dissolution of the capsule formulation, suggesting the need to avoid co-administration with antacids, H-2 blocker antihistamines and proton pump inhibitors.<sup>26,29</sup>

Terbinafine utilizes several pathways for its own metabolism and is an inhibitor of cytochrome 2D6 (CYP 2D6).<sup>30</sup> Drug interactions with terbinafine have been minimal to absent with no contraindications noted.<sup>21,30</sup>

Rifampin may significantly increase the metabolism of terbinafine and all azole antifungal agents, including itraconazole, thereby enhancing the risk of antifungal treatment failure.<sup>25,31</sup> Phenytoin and carbamazepine may decrease itraconazole serum levels through enzyme induction.<sup>25</sup>

## Evaluation and Monitoring Guidelines

**Disease-Related.** A method for tabulating the baseline status of onychomycosis prior to treatment is recommended. Photography may be utilized where available. It may be useful to place a groove within the nail plate at the proximal edge of visible disease and at the base of the plate just distal to the proximal nail fold, especially with larger nail plates such as the large toenail. This allows for an easier assessment of the extent of growth and progression of disease-free nail over time which can also be demonstrated to the patient. If response is lagging despite allowance for a sufficient amount of time to achieve a response (ie. 5 to 6 months), the clinician may then elect to "boost" therapy by initiating a short course of additional treatment.

Confirmation of diagnosis by laboratory evaluation using potassium hydroxide preparation, fungal culture and/or nail plate "biopsy" with PAS staining prior to initiation of treatment has been suggested in updated product monographs with itraconazole and terbinafine.<sup>25,31</sup> This dogmatic stance has been a matter of controversy; the most reasonable position is probably somewhere in between. It is justifiable to state that laboratory confirmation of a mycotic nail infection is the ideal scenario, precluding the inefficiency, risk and unwarranted cost of antifungal treatment in patients with onychodystrophies that are not onychomycosis.<sup>32</sup> Even in the case of topical therapy, such as with ciclopirox nail lacquer, usage in a patient who does not have onychomycosis is an inefficient and unnecessary expense.

Laboratory confirmation of onychomycosis is very dependent on obtaining an appropriate nail specimen and utilizing a

quality laboratory; specimens for direct microscopy and fungal culture achieve the greatest yield when subungual debris is obtained after trimming of onycholytic plate, preferably with a small curette.<sup>33-35</sup> Nail plate "biopsy" specimens are most helpful when then are full-thickness through the plate and not limited to only distal slivers.<sup>35</sup>

**Clinical.** A detailed medical and drug history is very important to detect a pre-existing history of congestive heart failure, hepatic disease or potentially significant drug interactions. After initiation of treatment, periodic clinical follow-up is recommended to monitor clinical efficacy, compliance and to observe for potential adverse reactions. The use of itraconazole or terbinafine for onychomycosis is generally not recommended in patients with pre-existing hepatic abnormalities, especially active or chronic disease.<sup>25,31</sup> The US product monograph also suggests that terbinafine is not recommended in patients with significant renal impairment (< 50 mL/min).<sup>31</sup>

**Laboratory Monitoring.** Although the risk of significant toxicities such as hepatotoxicity are rare with itraconazole and terbinafine, suggested guidelines serve to provide a comfortable and consistent baseline for the clinician. Based on US product monographs, pre-treatment (baseline) evaluation of hepatic enzymes is recommended prior to initiation of treatment with itraconazole and terbinafine.<sup>25,31</sup> This allows the clinician to screen for unknown pre-existing hepatic disease and possibly for findings suggestive of undisclosed alcohol ingestion. The decision regarding repetition of testing is made on a case-by-case basis by the clinician, based on factors related to the individual patient (ie. past medical history, use of other medications with hepatotoxicity potential, etc).

There are no specific recommendations regarding hematologic monitoring in patients treated with itraconazole for onychomycosis.<sup>25</sup> In patients with immune deficiency, the US product monograph suggests that a complete blood cell count should be considered in patients treated with terbinafine for greater than 6 weeks.<sup>31</sup>

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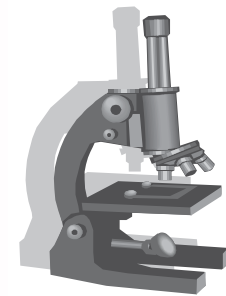
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\* Treatment success was defined as a Physician's Static Global Assessment score of 0 or 1, plus a plaque thickness score of 0, an erythema score of 0 or 1, and a scaling score of 0 or 1 at endpoint, scored on a severity scale from 0 to 3.

Reference: 1. Data on file (DOPCD-C-005), Connetics Corporation.

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# OLUX<sup>®</sup> Foam, 0.05% (clobetasol propionate)

R<sub>x</sub> only

## BRIEF SUMMARY

For Dermatologic Use Only

Not for Ophthalmic Use

**INDICATIONS AND USAGE** OLUX Foam is a super-potent topical corticosteroid indicated for short-term topical treatment of the inflammatory and pruritic manifestations of moderate to severe corticosteroid-responsive dermatoses of the scalp, and for short-term topical treatment of mild to moderate plaque-type psoriasis of non-scalp regions excluding the face and intertriginous areas. Treatment beyond 2 consecutive weeks is not recommended and the total dosage should not exceed 50 g per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. In a controlled pharmacokinetic study, some subjects experienced reversible suppression of the adrenals following 14 days of OLUX Foam therapy (See ADVERSE REACTIONS). Use in children under 12 years of age is not recommended. **CONTRAINDICATIONS** OLUX Foam is contraindicated in patients who are hypersensitive to clobetasol propionate, to other corticosteroids, or to any ingredient in this preparation. **PRECAUTIONS General:** Clobetasol propionate is a super-potent topical corticosteroid that has been shown to suppress the adrenals at 7.0 g of OLUX Foam per day. Lesser amounts of OLUX Foam were not studied. Systemic absorption of topical corticosteroids has caused reversible adrenal suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment. Manifestations of Cushing's syndrome, hyperglycemia, and glucosuria can also be produced in some patients by systemic absorption of topical corticosteroids while on treatment. Conditions which augment systemic absorption include the application of more potent steroids, use over large surface areas, prolonged use, and the addition of occlusive dressings. Patients applying a topical steroid to a large surface area or to areas under occlusion should be evaluated periodically for evidence of adrenal suppression. If adrenal suppression is noted, an attempt should be made to withdraw the drug, to reduce the frequency of application, or to substitute a less potent steroid. Recovery of HPA axis function is generally prompt upon discontinuation of topical corticosteroids. Infrequently, signs and symptoms of glucocorticosteroid insufficiency may occur requiring supplemental systemic corticosteroids. For information on systemic supplementation, see prescribing information for those products. Pediatric patients may be more susceptible to systemic toxicity from equivalent doses due to their larger skin surface to body mass ratios. See **PRECAUTIONS-Pediatric Use**. If irritation develops, OLUX Foam should be discontinued and appropriate therapy instituted. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing a failure to heal rather than by noting a clinical exacerbation, as with most topical products not containing corticosteroids. Such an observation should be corroborated with appropriate diagnostic patch testing. In the presence of dermatological infections, the use of an appropriate antifungal or antibacterial agent should be instituted. If a favorable response does not occur promptly, use of OLUX Foam should be discontinued until the infection has been adequately controlled. **Information for Patients:** Patients using topical corticosteroids should receive the following information and instructions: 1. This medication is to be used as directed by the physician and should not be used longer than the prescribed time period. It is for external use only. Avoid contact with the eyes. 2. This medication should not be used for any disorder other than that for which it was prescribed. 3. The treated area should not be banded or otherwise covered or wrapped so as to be occlusive unless directed by the physician. 4. Patients should report to their physician any signs of local adverse reactions. **Laboratory Tests:** The following tests may be helpful in evaluating patients for adrenal suppression: ACTH stimulation test; A.M. plasma cortisol test; urinary free cortisol test. **Carcinogenesis, Mutagenesis, and Impairment of Fertility:** Long-term animal studies have not been performed to evaluate the carcinogenic potential of clobetasol propionate. Clobetasol propionate was non-mutagenic in three different test systems: the Ames test, the *Saccharomyces cerevisiae* gene conversion assay, and the *E. coli* B WP2 fluctuation test. Studies in the rat following subcutaneous administration of clobetasol propionate at dosage levels up to 0.05 mg/kg per day revealed that the females exhibited an increase in the number of resorbed embryos and a decrease in the number of living fetuses at the highest dose. **Pregnancy: Teratogenic Effects: Pregnancy Category C:** Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. Some corticosteroids have been shown to be teratogenic after dermal application to laboratory animals. Clobetasol propionate has not been tested for teratogenicity by the topical route; however, it is absorbed percutaneously, and when administered subcutaneously, it was a significant teratogen in both the rabbit and the mouse. Clobetasol propionate has greater teratogenic potential than steroids that are less potent. Teratogenicity studies in mice using the subcutaneous route resulted in fetotoxicity at the highest dose tested (1 mg/kg) and teratogenicity at all dose levels tested down to 0.03 mg/kg. These doses are approximately 1.4 and 0.04 times, respectively, the human topical dose of OLUX based on body surface area comparisons. Abnormalities seen included cleft palate and skeletal abnormalities. In rabbits, clobetasol propionate was teratogenic at doses of 0.003 and 0.01 mg/kg. These doses are approximately 0.02 and 0.05 times, respectively, the human topical dose of OLUX based on body surface area comparisons. Abnormalities seen included cleft palate, cranioschisis, and other skeletal abnormalities. There are no adequate and well-controlled studies of the teratogenic potential of clobetasol propionate in pregnant women. OLUX Foam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.** **Nursing Mothers:** Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Because many drugs are excreted in human milk, caution should be exercised when OLUX Foam is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness of OLUX Foam in pediatric patients have not been established; therefore, use in children under 12 years of age is not recommended. Because of a higher ratio of skin surface area to body mass, pediatric patients are at a greater risk than adults of adrenal suppression and Cushing's syndrome when they are treated with topical corticosteroids. Pediatric patients are therefore at greater risk of adrenal insufficiency during and/or after withdrawal of treatment. Adverse effects including striae have been reported with inappropriate use of topical corticosteroids in infants and children. Adrenal suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema. **Geriatric Use:** Clinical studies of OLUX Foam did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. **ADVERSE REACTIONS** In a controlled pharmacokinetic study, 5 of 13 subjects experienced reversible suppression of the adrenals at anytime during the 14 days of OLUX Foam therapy to at least 20% of the body surface area. Of the 13 subjects studied, 1 of 9 with psoriasis were suppressed after 14 days and all 4 of the subjects with atopic dermatitis had abnormal cortisol levels indicative of adrenal suppression at some time after starting therapy with OLUX Foam. OLUX Foam is not indicated for non-scalp atopic dermatitis, as the safety and efficacy of OLUX Foam in non-scalp atopic dermatitis has not been established. Use in children under 12 years of age is not recommended. Systemic absorption of topical corticosteroids has produced reversible adrenal suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria in some patients (see PRECAUTIONS). In a controlled clinical trial (188 subjects) with OLUX Foam, in subjects with psoriasis of the scalp, there were no localized adverse reactions reported in the OLUX Foam treated subjects. In two controlled clinical trials (360 subjects) with OLUX Foam in subjects with psoriasis of non-scalp regions, localized adverse events that occurred in the OLUX Foam treated subjects included application site burning (10%), application site dryness (<1%), and other application site reactions (4%). In larger controlled trials with other clobetasol propionate formulations, the most frequently reported local adverse reactions have included burning, stinging, irritation, pruritus, erythema, folliculitis, cracking and fissuring of the skin, numbness of the fingers, skin atrophy, and telangiectasia (all less than 2%). The following additional local adverse reactions have been reported with topical corticosteroids, but they may occur more frequently with the use of occlusive dressings and higher potency corticosteroids such as OLUX Foam. These reactions are listed in an approximate decreasing order of occurrence: dryness, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, striae, and miliaria. **OVERDOSAGE** Topically applied OLUX Foam can be absorbed in sufficient amounts to produce systemic effects. See **PRECAUTIONS**. **DOSAGE AND ADMINISTRATION** Note: For proper dispensing of foam, hold the can upside down and depress the actuator. OLUX Foam should be applied to the affected area twice daily, once in the morning and once at night. Invert the can and dispense a small amount of OLUX Foam (up to a maximum of a golf-ball-size dollop or one and a half capfuls) into the cap of the can, onto a saucer or other cool surface, or to the lesion, taking care to avoid contact with the eyes. Dispensing directly onto hands is not recommended (unless the hands are the affected area), as the foam will begin to melt immediately upon contact with warm skin. When applying OLUX Foam to a hair-bearing area, move the hair away from the affected area so that the foam can be applied to each affected area. Pick up small amounts with fingertips and gently massage into affected area until the foam disappears. Repeat until entire affected area is treated. Apply the smallest amount possible that sufficiently covers the affected area(s). No more than one and a half capfuls of foam should be used at each application. Do not apply to face or intertriginous areas. OLUX Foam is a super-high-potency topical corticosteroid; therefore, treatment should be limited to 2 consecutive weeks and amounts greater than 50 g/week should not be used. Use in pediatric patients under 12 years of age is not recommended. Unless directed by a physician, OLUX Foam should not be used with occlusive dressings. **HOW SUPPLIED** OLUX Foam is supplied in 10 g (NDC 63032-031-00) and 50 g (NDC 63032-031-50) aluminum cans. Store at controlled room temperature 68-77°F (20-25°C). **WARNING: FLAMMABLE. AVOID FIRE, FLAME OR SMOKING DURING AND IMMEDIATELY FOLLOWING APPLICATION.** Keep out of reach of children. Contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120°F (49°C).

Manufactured for: Connetics Corporation, Palo Alto, CA 94303 USA

By: Miza Pharmaceuticals (UK) Limited, Runcorn WA7 1NU, United Kingdom

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# Observational Use of Pimecrolimus 1% Cream: Clinical Results and Applications Based on a Large Private Practice Experience

Richard Diskin, D.O., James Q. Del Rosso, D.O., FAOCD, Saul Schreiber, D.O.

Pimecrolimus 1% cream is a non-steroidal calcineurin inhibitor approved in the United States for treatment of atopic dermatitis. Available studies demonstrate anti-inflammatory activity through inhibition of cytokine production and release from activated T lymphocytes.<sup>1,2</sup> As compared to cyclosporin and tacrolimus, based on various laboratory models, pimecrolimus has been reported to demonstrate greater skin selectivity, comparable or superior anti-inflammatory activity and less immunosuppressive activity.<sup>1-3</sup> Efficacy and safety have been demonstrated in short (6 weeks) and long-term (12 months) studies in adult and pediatric patients (age 3 months to 17 years) with atopic dermatitis.<sup>1,2,4-8</sup> Although FDA-approved for the treatment of mild to moderate atopic dermatitis, efficacy has also been demonstrated in patients with severe disease.<sup>1,2,4-8</sup> As systemic absorption is usually undetectable or negligible with chronic administration, pimecrolimus use is continued until clearance of disease is achieved and restarted at the immediate onset of signs and symptoms.<sup>3,6-8</sup> Maintenance therapy with pimecrolimus 1% cream has been shown to be topical steroid-sparing.<sup>6-8</sup>

The rapid population growth of the Las Vegas, Nevada community has resulted in an observed increase in allergic-related disorders, including atopic dermatitis, presenting to practicing clinicians. Disease flares are common throughout the year, due to construction-related airborne dust circulation and intermittent wind storms, dry desert climate exacerbating xerosis and epidermal barrier disruption, intermittent abrupt temperature fluctuations and increased foliage (ie. residential and commercial landscaping, golf courses) increasing release of airborne allergens.

A multicenter observational evaluation was initiated in February 2002 examining open-label usage of pimecrolimus 1% cream for eczematous dermatitis including atopic dermatitis, and other applications ("off label" uses) including hand eczema, chronic intermittent eyelid dermatitis, psoriasis, vitiligo and seborrheic dermatitis. Tabulated results include global evaluation of efficacy, patient assessment of timing of improvement in signs and symptoms of disease, definition of usage as monotherapy or in combina-

tion with other therapies, adverse reactions and evaluation of previous therapies. The goal of the evaluation is to report "real world" experience reflective of private practice usage from three separate general dermatology offices, of pimecrolimus 1% cream in adults and children in order to (1) better define optimal clinical applications and limitations of therapy and to (2) evaluate consistencies and differences as compared to controlled, pivotal trials. Reported results include experience documented between February 2002 – January 2003.

## Observational Evaluation

At the initial encounter, the following information was documented:

- Patient name / date of birth
- Total duration of disease
- Duration of disease
- Past medical history
- Family history
- Previous therapies used
- Clinical presentation
- Anatomic sites affected
- Symptoms / severity (rated by patient as mild, moderate, severe)
- Overall disease severity (rated by physician as mild, moderate, severe)
- Recommended skin care products (ie. cleansers, emollients)
- Recommended therapy (pimecrolimus cream + any other medications prescribed)
- Follow-up instructions

At follow-up visit(s), the following information was documented:

- Response to therapy
  - o visible eruption (improvement rated by physician as completely cleared, moderate, minimal or none)
  - o symptoms ie. pruritus (improvement rated by patient as completely resolved, moderate, minimal or none)
- Resistant anatomic sites

- Tolerability
- Adverse reactions
- Stoppage of any medications
- Changes in therapy
- Follow-up

In all patients, topical pimecrolimus 1% cream was applied twice daily. The term "combination therapy" refers to concomitant use of pimecrolimus 1% cream twice daily and a specified topical corticosteroid agent applied twice daily after application of topical pimecrolimus or once daily at bedtime.

Patient follow-up was based on instructions given at the discretion of the physician at each encounter consistent with what would be recommended in a private practice scenario. The pediatric age range was defined as 16 years of age or less. Patients included in the analysis were instructed to utilize specific basic skin care products selected by the treating dermatologist while undergoing therapy. The choices included branded cleansers and emollients recognized to exhibit a low risk of associated irritation. Follow-up therapy after the initial visit was usually scheduled for 2 – 4 weeks.

## Results

A total of 300 patients were treated with pimecrolimus 1% cream twice daily with or without other concomitant therapies for a variety of dermatologic presentations. In previously treated patients, all were off of any prescription therapy related to their skin condition for at least two weeks prior to presentation. The disease states treated were as follows:

- Atopic Dermatitis (children) 50% (34% mild / 56% moderate / 10% severe)
- Atopic Dermatitis (adults) 20% (91% moderate / 9% severe)
- Recurrent Hand Eczema (adults) 10% (subacute or chronic presentations)
- Idiopathic Scrotal Pruritus (adults) 2% (early lichen simplex)
- Recurrent Eyelid Dermatitis (adults) 10% (subacute or chronic presentation)
- Seborrheic Dermatitis (adults) 5%

(face, periauricular)

- Other Disease States 3%

Alopecia Areata  
5 patients (discoïd scalp patches)

Psoriasis (adults)  
2 patients (localized)

Vitiligo (adults)  
2 patients (localized)

## Atopic Dermatitis

**Pediatric Group.** One hundred-fifty children (81 females / 69 males) with atopic dermatitis were treated with pimecrolimus 1% cream twice daily. Clinical presentation included involvement of the face (17%), neck (16%), extremities (96%) and trunk (67%).

**Mild disease:** In patients with mild disease, pimecrolimus 1% cream was utilized as monotherapy in 73% of cases; the remainder were prescribed a low to mid potency topical corticosteroid to use once or twice daily during the first 1 – 2 weeks of treatment. In those receiving pimecrolimus 1% cream alone, 79% reported resolution of pruritus within 1 week and 86 % reported marked or complete clearance of the eruption within the first 2 – 4 weeks. In those using initial combination therapy, 94 % experienced resolution of pruritus within in 1 week and marked or complete clearance of the eruption within 2 – 4 weeks or less. One report of mild transient burning was noted after application of topical pimecrolimus alone over the first few days of use; this did not result in discontinuation of therapy.

**Moderate disease:** Forty-four percent of patients with moderate disease used pimecrolimus 1% cream twice daily as monotherapy; the remainder used combination therapy with a mid-potency topical corticosteroid once or twice daily during the first 1 – 2 weeks of treatment. In those receiving pimecrolimus 1% cream alone, 71% reported marked improvement or resolution of pruritus within 1 - 3 weeks and 73% reported marked or complete clearance of the eruption within the first 2 – 4 weeks. In those using initial combination therapy, 86% reported marked improvement or resolution of pruritus in 1 – 2 weeks and 87% demonstrated marked or complete clearance of the eruption within 2 – 4 weeks. Five reports of mild transient stinging or burning were noted after application of topical pimecrolimus therapy; therapy was continued.

**Severe disease:** The patients presenting with severe disease were all treated with pimecrolimus 1% cream in combination with a mid or high potency topical

corticosteroid.

One patient also received a 7 day course of oral prednisolone. Marked improvement or clearance of pruritus was seen in 70% of patients within the first 1 – 3 weeks and 60% demonstrated marked improvement in the eruption within 2 – 4 weeks. The remainder demonstrated a slower response and additional adjustments in therapy. Two cases of local intolerance were noted, described as burning or stinging, that did not result in interruption in treatment.

**Maintenance therapy:** In all groups, once control was achieved, pimecrolimus 1% cream was used as monotherapy to maintain remission with therapy initiated at the immediate onset of disease signs (ie. erythema) or symptoms (pruritus). Topical corticosteroid therapy was used to control flares, usually with a mid potency agent.

**Adult Group.** Sixty adult patients (34 males / 26 females) presented with atopic dermatitis and were treated; areas of involvement included the neck (20%), extremities (85%) and trunk (70%).

**Moderate disease:** In patients with moderate disease, pimecrolimus 1% cream was utilized as monotherapy in 50 % of cases; the remainder were prescribed a mid potency topical corticosteroid to use once or twice daily during the first 1 – 2 weeks of treatment. In those receiving pimecrolimus 1% cream alone, 65 % reported resolution of pruritus within 1 week and 75 % reported marked or complete clearance of the eruption within the first 2 – 4 weeks. In those using initial combination therapy, 80 % experienced resolution of pruritus within 1 week and marked or complete clearance of the eruption within 2 – 4 weeks. Two patients treated with topical pimecrolimus alone reported transient stinging after application that did not result in discontinuation in treatment.

**Severe disease:** The patients presenting with severe disease were all treated with pimecrolimus 1% cream in combination with a high or ultra-high potency topical corticosteroid. Marked improvement or clearance of pruritus was seen in 70 % of patients within the first 1 – 2 weeks and 70% demonstrated marked improvement in the eruption within 2 – 4 weeks. The remainder demonstrated a slower response and required additional adjustments in therapy. No adverse reactions were reported.

**Maintenance therapy:** Once control was achieved, pimecrolimus 1% cream was used as monotherapy to maintain remission in 60% of patients. Therapy was initiated at the immediate onset of

disease signs (ie. erythema) or symptoms (pruritus). Mid-potency topical corticosteroid therapy was used to control flares. The remainder maintained control of atopic dermatitis using intermittent topical corticosteroid treatment alone, initiated at the onset of a flare.

## Recurrent Hand Eczema

Thirty adults (16 females / 14 males) with recurrent subacute hand eczema were treated. In all cases combination therapy with a mid-potency topical corticosteroid was used. The topical corticosteroid was used either after application of pimecrolimus 1% cream twice daily or prior to bedtime. Forty percent of patients reported improvement in visible eruption and decrease in pruritus with combination therapy as compared to previous therapy with topical corticosteroid alone. Although data was too limited to assess the role of pimecrolimus therapy in combination with topical corticosteroid use in this patient group, reported responses suggested benefit in some patients. The role of topical pimecrolimus as monotherapy in this patient population requires further investigation. No adverse reactions were reported.

## Idiopathic Scrotal Pruritus

Six adult males with idiopathic persistent-recurrent scrotal pruritus present for at least 6 months were treated with topical pimecrolimus 1% cream twice daily as monotherapy. Three patients had previously used low or mid potency topical corticosteroid therapy with success followed by recurrence. The only clinical features were early lichen simplex without any evidence of other primary skin findings. All six patients demonstrated marked improvement or resolution within 2 - 4 weeks of therapy with pimecrolimus 1% cream. Due to the chronicity of disease and involvement at a naturally occluded anatomic site where topical corticosteroids may be associated with cutaneous atrophy after prolonged use, pimecrolimus therapy was continued to maintain disease control. No adverse reactions were reported.

## Recurrent Eyelid Dermatitis

Thirty adult patients (27 female / 3 male) presenting with eyelid dermatitis recurring intermittently over a period of at least 1 – 2 years were treated with topical pimecrolimus as monotherapy. In 90 % of patients, marked improvement or complete resolution of the visible eruption and pruritus were noted within 7 – 10 days or less. The remainder required the addition of a short course (< 1 week) of low to mid potency topical corticosteroid therapy for

control. No adverse reactions were reported.

## Seborrheic Dermatitis

Fifteen adult patients (13 males / 2 females) with recurrent seborrheic dermatitis involving the face and/or periauricular region were treated with topical pimecrolimus alone. In 80% of patients, the visible eruption and pruritus resolved within 7 – 10 days or less. The remainder cleared using either a short course of medium potency topical corticosteroid therapy or topical sulfacetamide-sulfur topical suspension. No adverse reactions were reported.

## Other Disease States

Alopecia areata. Two adult females and one female child with scattered patches of scalp alopecia areata were treated with topical betamethasone valerate 0.12% foam followed by topical pimecrolimus twice daily. The two adult patients developed significant regrowth rated as 75% and 60% within 4 – 6 weeks. The female child exhibited partial regrowth (rated as 50% improvement) within 4 weeks. One male child demonstrated complete regrowth of hair within an isolated patch of scalp alopecia areata within 8 weeks using topical pimecrolimus as monotherapy. One adult female patient treated with a ultra-high potency topical corticosteroid in combination with topical pimecrolimus demonstrated no response to treatment after one month. None of the patients exhibited an ophiasis pattern. Further study is needed to evaluate the role of topical pimecrolimus in alopecia

areata.

Psoriasis. Two patients with plaque psoriasis localized to the extremities were treated with topical pimecrolimus alone. One adult male with bilateral elbow involvement had developed a decreased response to a high potency topical corticosteroid that had been previously effective. Tachyphylaxis was suspected. In this patient, a frictional component (Koebner's phenomenon) was also suspected. Topical pimecrolimus as monotherapy without occlusion produced significant improvement within 6 weeks. A second male patient with chronic plaque psoriasis involving the knees demonstrated little to no improvement with topical pimecrolimus therapy. The role of topical pimecrolimus in the treatment of various clinical presentations of psoriasis warrants further study.

Vitiligo. One adult female patient with small scattered patches of vitiligo on the upper extremities demonstrated significant partial repigmentation within 3 months of topical pimecrolimus monotherapy. A second adult female patient with extensive vitiligo on the dorsum of the hands exhibited no improvement.

## Conclusions

An open evaluation in 3 private practice centers support the following conclusions:

- Topical pimecrolimus 1% cream applied twice daily was effective and well tolerated when used as monotherapy in patients with mild to moderate atopic dermatitis in adults and children.

- The use of combination therapy with topical pimecrolimus and topical corticosteroids demonstrated significant efficacy in patients with all severities of atopic dermatitis and was well tolerated. Whether or not the combination therapy approach provides additive or synergistic therapeutic benefit would require a properly designed, controlled evaluation.

- There was no apparent antagonistic effect or associated local adverse reactions associated with a short term combination therapy approach (less than 4 weeks). Although case numbers are limited, combination therapy may be of benefit in some patients with alopecia areata.

- Topical pimecrolimus therapy was effective in the management of idiopathic scrotal pruritus, recurrent eyelid dermatitis and seborrheic dermatitis.

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# Local Reaction to Black Ink in a multi-colored Permanent Tattoo

Scott J.M. Lim, DO, Joseph Nellis, BS

## Abstract

A 26 year old female presented to the clinic complaining of discomfort and irritation involving a recent tattoo on her upper arm. A papular reaction on an erythematous base was noted involving the black colored areas of a circumferential blue, red and black colored permanent tattoo on her upper left arm. The clinical diagnosis made consisted of allergic contact/foreign body dermatitis secondary to black pigment with possible localized infectious component. A case report and literature review of reactions to black permanent tattoo ink follows. Literature reviewed utilizing the PubMed search engine with key words: tattoo, reaction, black ink, and laser in varied combinations.

## Introduction:

Tattooing is a common art in the western world. Many tattoo related reactions have been reported, therefore, it is likely that a physician or surgeon will encounter patients having reactions of some fashion to a tattoo. The vast majority of reported reactions to tattoos have been involving temporary tattoos and also permanent tattoos associated with colored inks such as red, blue and green. Few reports are found in literature involving black permanent ink reactions. We describe one such reaction to black ink in a permanent tattoo and discuss other reported black ink reactions in permanent tattoos as well as treatment options available.

## Case Report:

A 26 year old white female with no previously known allergies, and in good general health, reported to clinic complaining of discomfort and irritation at the site of a permanent tattoo which was placed three weeks earlier. The tattoo was a circumferential band of blue, black and red of about two centimeters in width located around her left upper arm.

Examination revealed erythema as well as a yellow/green papular eruption only in black pigmented areas. Red and blue areas of the tattoo were unremarkable (Figure 1). Axillary lymph nodes were not palpable.

Biopsy was not performed at this time due to the patient's wishes to preserve the tattoo and try conservational therapy first. The clinical diagnosis made consisted of allergic contact/foreign body dermatitis secondary to black pigment with possible localized infectious component.

Treatment consisted of oral cephalexin 500 milligrams twice daily for ten days and 0.1% hydrocortisone butyrate cream applied twice daily.

Upon follow-up nine days later, the

affected areas demonstrated complete resolution. Only minor hypopigmentation within the black pigmented areas (Figure 2) remained. Topical steroid usage was discontinued at that time. Patch testing was offered upon follow-up, however, the patient declined.

## Comment:

It has been estimated that 3-5% of the western population have tattoos<sup>1</sup>. We can intuitively assume that in certain subsets of the population, this percentage may be higher. From data collected in 1999, Dr. Stephens found that 27% of U.S. Marine Corps and Air Force recruits have tattoos<sup>2</sup>. Data collected in 1995-1996 suggests that 4.5% of adolescents had a tattoo<sup>3</sup>. American Family Physician reports a poll published in American Academy of Pediatrics News that found one in ten adolescents had a tattoo and 55% of the remaining were contemplating getting one<sup>4</sup>. Therefore, we should expect to see tattoo allergies at a higher incidence in certain subsets of the population, such as in the military and adolescent groups.

Regardless of the exact numbers, it is clear that tattooing is common in our society yet there is surprisingly little published literature found concerning reactions to black permanent tattoos.

A literature search for reported cases of allergic reactions to permanent black tattoo ink revealed a case of pruritic erythematous papules in and around an India Ink tattoo which was only partly responsive to topical steroid therapy<sup>5</sup>.

A similar case to ours was reported consisting of a perilesional pruritis, edema and erythema with crusts and papulovesicals, which resolved following treatment with topical 1% hydrocortisone plus five days of oral clarithromycin<sup>6</sup>.

Doctor Goldberg reported a generalized lichenoid reaction (pruritic macular



Figure 1



Figure 2

rash) localized to a black, blue, green and red pigmented tattoo, which reoccurred following steroidal treatments and was surgically removed. The patient continued to suffer from reduced intensity reoccurrences, which were controlled with oral steroid therapy<sup>7</sup>.

In another report, a foreign body granulomatous type reaction occurred to the black pigment of tattoos placed ten years earlier. In this case, the inflamed and pruritic reaction responded well to 0.05% difflorason diacetate applied twice daily<sup>8</sup>.

Some unique conditions have also been described relating to permanent tattoo black dye. Doctor Jacob describes a case of guttate psoriasis erupting one week following placement of a permanent black tattoo on the upper arm<sup>9</sup>. A morphea-like reaction was reported involving a green, purple and black tattoo<sup>10</sup>. Systemic and pulmonary sarcoidosis present-

ing via tattoo reactions has also been described<sup>11-12</sup>.

From the cases reviewed, we can see that reactions to black permanent tattoo dye do in fact occur. The reactions may be self limiting or may be progressive. Some reactions may require more than one treatment, may reoccur, or may require removal via surgery or laser. We initiated conservative therapy in our case, which fortunately cleared.

## Conclusion:

Tattoo reactions may resolve spontaneously, clear with conservative treatment, reoccur or become chronic, or they may become severe and/or systemic. This can pose a dilemma when trying to determine the patient's prognosis and decide on management. Biopsies can assist in diagnosis, however, it would require some degree of destruction to the artwork which may not be desired by the patient. Cultures of wounds may help diagnose or exclude infections, however, open wounds would expectedly grow normal skin flora, therefore, may be less helpful. Patch testing can help identify the causative agent, however, obtaining information from ink manufacturers concerning ingredients may be difficult, as well as obtaining exact lot and manufacturer samples from the tattoo artist. In addition, the patient may find patch testing economically and logistically cumbersome. These dilemmas can impede meaningful patch testing and without knowledge of exact allergens, it can be difficult to foresee future reactions with tattoos. Our patient was not deterred from pursuing additional tattoos despite being advised of the risk for future allergy reactions.

The physician confronting a tattoo reaction may have to make treatment decisions based solely on clinical presentation, as in our case. We suggested conservative management initially. Other possibly useful strategies might include adding an antihistamine and/or utilizing oral steroids for more generalized or persistent reactions. One may also consider the addition of an immunomodulator as well, such as tacrolimus or pimecrolimus. Bacterial cultures and/or biopsy may be useful to further direct treatment as well. We did neither culture nor biopsy, how-

ever, their utility is recognized. Biopsy recommendations may be difficult to justify for localized, less involved reactions, due to the destruction of the artwork, however, we recommend they be offered in order to assist in diagnosis and exclude other pathology. Bacterial cultures would naturally help adjust antimicrobial therapy if a causative organism was found.

Persistent, severe, atypical dermatoses and/or reoccurrences may require removal. Tattoos can be removed via surgical excision or via laser. Surgical removal would be the surest and quickest way for removal of a tattoo instigating a reaction, but would result in surgical scars and may not be feasible due to the size and location of the tattoo. Laser treatment may be a better approach if the area to be excised is too large or anatomically not advisable to excise, however, multiple laser treatments may be required to remove the tattoo<sup>13-14</sup>.

There are relatively few reports found in our literature search concerning the ability of lasers to resolve persistent tattoo allergies. Of those reported, the successful treatments involved reactions to red ink<sup>15,16,20</sup>. Successful treatment of a lichenoid reaction<sup>15</sup> and a flaky pruritic reaction<sup>16</sup> has been published with no complications noted. On the other hand, there has been a report of a local eczematous tattoo reaction involving green and yellow dyes evolving into generalized urticaria for three months following laser treatment<sup>17</sup>. Other reports of reactions following laser treatment of tattoos involve elective treatments of non-reactive tattoos. These dermatoses range from localized reactions following treatment of a multicolored tattoo<sup>18</sup> to more generalized reactions such as urticaria and diffuse papular pruritis<sup>19</sup>. However, laser removal can be targeted to certain colors and does not leave a scar as would other removal methods. It has been published that re-tattooing of a previously laser removed tattoo due to allergic reaction may be successfully accomplished with a different colored ink<sup>20</sup>. Therefore, laser removal may be a more desirable option for the reasons already stated, or for those who wish to retain as much of their artwork as possible or simply refuse surgery as an option. Due to the risks and complications inher-

ent with both surgery and laser removal, we suggest that the patient be as involved and informed as possible about the options available.

Given the popularity of tattoos and the likelihood for tattoo reactions, we look forward to more reports regarding types of reactions, possible prognostic indicators, treatment options and treatment outcomes in the future.

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# Tips For a Smooth Running Dermatology Practice

Jay S. Gottlieb, D.O., F.O.C.O.O.

## Abstract

Presented are some office tips that have been implemented to help the author run two busy offices over a 20 year career. Many of these tips may help you better manage your practice.

I began my own practice in 1982. Previously, I had worked with some very smart physicians. Let me preface this article by stating that I have not had an original idea or thought in my entire life. Everything is copied or borrowed. Many of these tips that I am about to relay to you were copied from Dr. Warren Brandes, Dr. Henry Sonnenshein and Dr. Michael Sherbin, who were my otolaryngology trainers. Other tips were taken from Dr. Art Lieberman and Dr. Terry Podolsky, with whom I worked part-time in a family practice in Michigan. They taught me a lot of "business medicine". Dr. Murray Zedeck gave me my post doctorate training in "business medicine" over many lunch dates here in south Florida. It gives me great pleasure sharing these tidbits of information with my colleagues. Here we go....these are tips that have helped me manage my practice:

## TIP 1

-Refer to a 'reception area' not a 'waiting room'. Nobody likes to wait.

## TIP 2

-Keep patients informed of approximate time until they will be seen.

I realized how important this really was one day at an airport. I arrived on time at my departure gate and the sign said 'Delayed'. It did not say how long the delay would be. When I asked the gate personnel how long the wait might be, all they would say is the flight is delayed and they didn't know how long it might be. I was stuck! No options. If they would have said 2 hours, I may have left the airport and went home; if it was an hour I could have gone to the airport restaurant and had lunch. I learned for this experience. From that day on, I had my front office staff walk into the reception area (not talk through the sliding glass windows) whenever I was more than 20 minutes behind schedule. They would announce to all of the patients that I was running behind by whatever the period of time that I was delayed. The patients were then given 3 options: 1) they could continue to wait, 2) they could go to the diner across the street for coffee and a doughnut on us and come back or 3) they could reschedule their appointment. It was amazing how this improved our office! We put the decision on the patient and they now had a choice. Less disgruntled patients. That's a good thing!

## TIP 3

-Answering the phone. I instituted this phrase "Doctors office, this is Mary, how may I direct your call?" No more "please hold" or "may I put you on hold". Nobody likes to wait and nobody likes to be placed on hold. They don't mind being

"directed". So no matter what the patient's reply is to "Doctors office, this is Mary, how may I direct your call?" your office staff has the opportunity to place that patient on hold as they are 'directed'. Think about it! What a simple idea.

## TIP 4

-Recall cards. Have 3 by 5 recall cards to remind patients of their appointments. These cards can be used to remind the patient to make an appointment (maybe an annual exam appointment) or it may actually have the time and date of an upcoming appointment. Have the patient address the card themselves at the checkout window. Place them into an index card file system under the month you wish to send out the reminder. You will have less no shows and more patients calling to inform you that they have a conflict in their schedule. The net result is less open slots in your schedule.

## TIP 5

-Flag system-For a one or two doctor office the flag system works well. These are inexpensive plastic flags that flip out and are attached to the wall next to each exam room door. You can get them with anywhere from 2 to 10 colored plastic flags.

Interpretation of the flags:

- \* No flags protruding signify a clean room
- \* Red flag means there is a patient in the room
- \* Green flag means it's a new patient (you may introduce yourself differently to a new patient!)

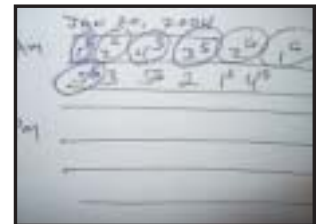
If you have 4 rooms then the blue flag could be the



first room to see, the yellow flag could be the second room to see, etc. If there are two doctors in the office then each doctor can get their own colored flag. It sounds complex but there is no confusion as to which patient is next. The system is learned by all very quickly. An example would be that a room with a red, green and blue flag would easily tell you that that room has a patient in it, that the patient is a new patient and that patient is the next to be seen. When the doctor walks into that room he or she flips all but except the red flag and that will signify that there is a patient in that room.

## TIP 6

-Rack/Jot System-This works for a practice with 2 or more doctors. Here, when a patient is placed in a room, their chart is placed in a rack near the doctor/nurse station or on the patient's door. A blank sheet of paper is taped to the counter at the doctor/nurse station. This paper is used for the entire day. When a patient is placed in a room, that room number is then written on that piece of paper. If the patient needs to see a particular physician, then the initial of that physician is placed next to the room number on that piece of paper.



When the doctor looks at the paper, he or she immediately knows which patient they are to go to see next. If the patient agreed to see the first available doctor, then only the room number, with no doctor's initials, is jotted down on the piece of

paper. The next available doctor would simply put his or her initial next to the room number and circle it and then proceed to that room. If office personnel need to know where any particular doctor is at any given time, all they need to do is look at this piece of paper taped on the counter at the doctor/nurse station and they will see which room was last circled by any given physician. Too easy!

### TIP 7

-Office reflection policy- This is what your office says about you! Assign specific office personnel to these tasks. Personnel can change tasks weekly. One checks the dates on the magazines in the reception area (patients may equate the aged reading material in your reception area with how well you keep up with your own medical journals!) The same person checks the reception area at least 3 times during the day for cleanliness. One person checks the restrooms for cleanliness at least 3 times a day. All personnel (including doctors) pick up pieces of paper that may be on the floor in common area or in exam rooms. All personnel must know that each exam room must be clean and no dirty instruments left in the exam room before a patient is escorted into that room.

### TIP 8

- Evaluation cards. Don't be afraid to evaluate your practice. These cards can be carried in your pocket. They are stamped and self addressed back to a post office box that you or your spouse should pick up every week or so. Don't allow your staff to pick these up! They may get tossed if they don't like what they see! The card should address:

- Did the physician take appropriate interest in them and their medical condition?
- Did they feel like the physician understood their concerns and what was their perceived quality of care?
- What was their experience with the checkout process?
- How would they rate their overall experience in your office?
- Ask if they would feel comfortable referring a friend or family member to your office ?
- How quickly was their call was answered when they called to make the appointment?
- How long were they placed on hold?
- How long it took to get an appointment?
- How clear the directions were to the office?
- Was parking adequate ?

- Were they greeted in a courteous fashion?

- Was the reception area clean and comfortable?

- Were they informed of how long the wait would be until seen by the physician?

- How long did they have to wait before they were seen by the physician?

These inquires can be scored on a 1 to 10 numeric basis. You, the physician, should hand the patient this survey card when you complete your visit and personally ask them to please complete this card honestly and send it back. Explain that this is very important to you and will help you make your office better for your patients. I experienced over a 90% response rate when I surveyed my patients in this manner. The alternative is to run your practice on the hope that things are going well. You can also utilize 'mystery shoppers' to test your offices phone etiquette and how well your office is doing with your initial contacts by phone. You can judge the number of rings until their call is answered, if employees identify themselves appropriately, the hold time, level of professionalism and overall perception. There are companies that you can hire to do all sorts of office evaluations to help assure that you, in fact, are running an efficient and courteous office.

### TIP 9

-Outsource! Various tasks in your practice are critical and need to be done efficiently. If you find that certain areas continuously fall behind and they are having a negative impact on your practice, you should consider outsourcing that task. This may be billing, cleaning the facility or transcriptions. I have instituted outsourcing transcriptions. I found that I was running further and further behind in my transcriptions. There were many times that I would either receive a call from a patient or see a patient back in the office and my transcription was still not back on the chart. This was having a negative impact on patient care and also making me look bad when I had to ask the patient what medications I (or my associates) had placed the patient on.



I interviewed several "overnight" transcriptions services. I eventually settled on a company called GL Transcriptions (561-998-1981). They guaranteed a 24 hour turn around time. I now dictate into a digital recorder. I am able to use macros (say a phrase that can trigger a paragraph of dictated script!). I download

them via the internet at the end of the day. By the next morning an entry level office staff member is able to print each dictation and have it on the chart by noon! Boy do I look good now! Talk to Gary at GL Transcriptions, he got me off to a very smooth transition with this new system.

### TIP 10

- Account for each and every patient encounter form (superbill). Have each encounter form sequentially numbered. If a patient pays cash or sometimes even with a check ("that's okay, I will just stamp the doctors name on your check!") and that superbill gets tossed then you will be out of a lot of money, or worse, out of business! Account for each superbill. I had an assigned staff member put the superbills in order at the end of each day. It would take this entry level person about 45 minutes to perform this task. It made accounting for superbills quite easy. It was to clear to the entire office personnel that this aspect of the practice was under close scrutiny.

### TIP 11

- Hold office personnel meetings on a regular basis. The doctors must attend these meetings! If the meetings are to be seen as important to the office staff (which they are!), then the doctors must be present to listen and to have input.

### TIP 12

-Respect and thank your office staff. Each member of the office staff is an important link of the chain that makes your practice work. Every link is important and must be appreciated and recognized fully for what they contribute to the overall success of the practice. I came to understand this important concept in the operating room. If an orderly did not properly prepare the patient and bring them to the operating room or if the employees in the instrument room did not care for the surgical instruments appropriately, then the operation about to be performed would not have a successful outcome. I was the surgeon, but I was useless without the other members of the surgical team. It always amazed me when a surgeon was abusive with the operating room personnel. The same is true in our offices! Each member needs to be recognized for their contribution to the practice in order to have an efficient and orderly practice.

### TIP 13

-Don't do it for the money! Early in my career, Dr. Barbara Ross Lee, one of my mentors, told me to always keep my priorities in order. She told me that I needed to look forward to going to work each day, but, more importantly, that I needed to look with greater anticipation to leaving work and going home at the end of each

day. There was a lot of wisdom in that suggestion. In my first year of practice I did about 12-15 facelifts. In my opinion (I am usually my own worst critic) my results were very good. But, I found the procedure quite boring and that I really didn't like working with that particular patient mix. I decided that rhytidectomy was one procedure that I would discontinue performing. The bottom line is that I really didn't enjoy the procedure or that patient mix. Design your practice so that you enjoy what you do. There will always be some things that we don't enjoy doing and yet we need to do them (for me, in

otolaryngology it was cerumin impactions and dermatology, it is the tearful female patient with diffuse hair loss at 4:45pm). Bottom line, limit what you don't enjoy doing. The money just isn't worth it!

Now that I have presented these 13 tips to running a smooth operation, I feel more at peace with myself. After all these years of impressing my friends, family and colleagues with my ability to have created an enjoyable and smooth running practice, I have come clean! I have openly and publicly admitted that none of my success in practice was of my own

doing. I copied and borrowed as I went along. Shameful? Not really. Success does leave a trail. Talk to people that are having the type of success that you want in your practice and in your life. It's amazing when you ask a successful person how they did it, they will be more than happy to talk to you about their success. As they say, "Just do it!"

*Contact Information:*  
Jay S. Gottlieb, D.O.  
3700 N. 32nd Terrace  
Hollywood, FL 33021  
Jay1953@aol.com

## IN THE TREATMENT OF ACNE...

Patient treated with TAZORAC® Cream 0.1% q.d.



BASELINE



WEEK 12

These unretouched photographs represent actual clinical experience with TAZORAC® Cream 0.1%. However, as with all medications, results may vary.

# The difference is in the results.

### FAST

- By week 4, a significantly greater reduction in comedones, 21% vs 14% for vehicle ( $P \leq .05$ )<sup>1</sup>

### POTENT

- 46% reduction in open and closed comedones by week 12 vs 27% for vehicle ( $P \leq .001$ )<sup>1</sup>
- 41% reduction in inflammatory acne by week 12 vs 27% for vehicle ( $P = .01$ )<sup>1</sup>

### ELEGANT

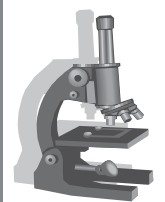
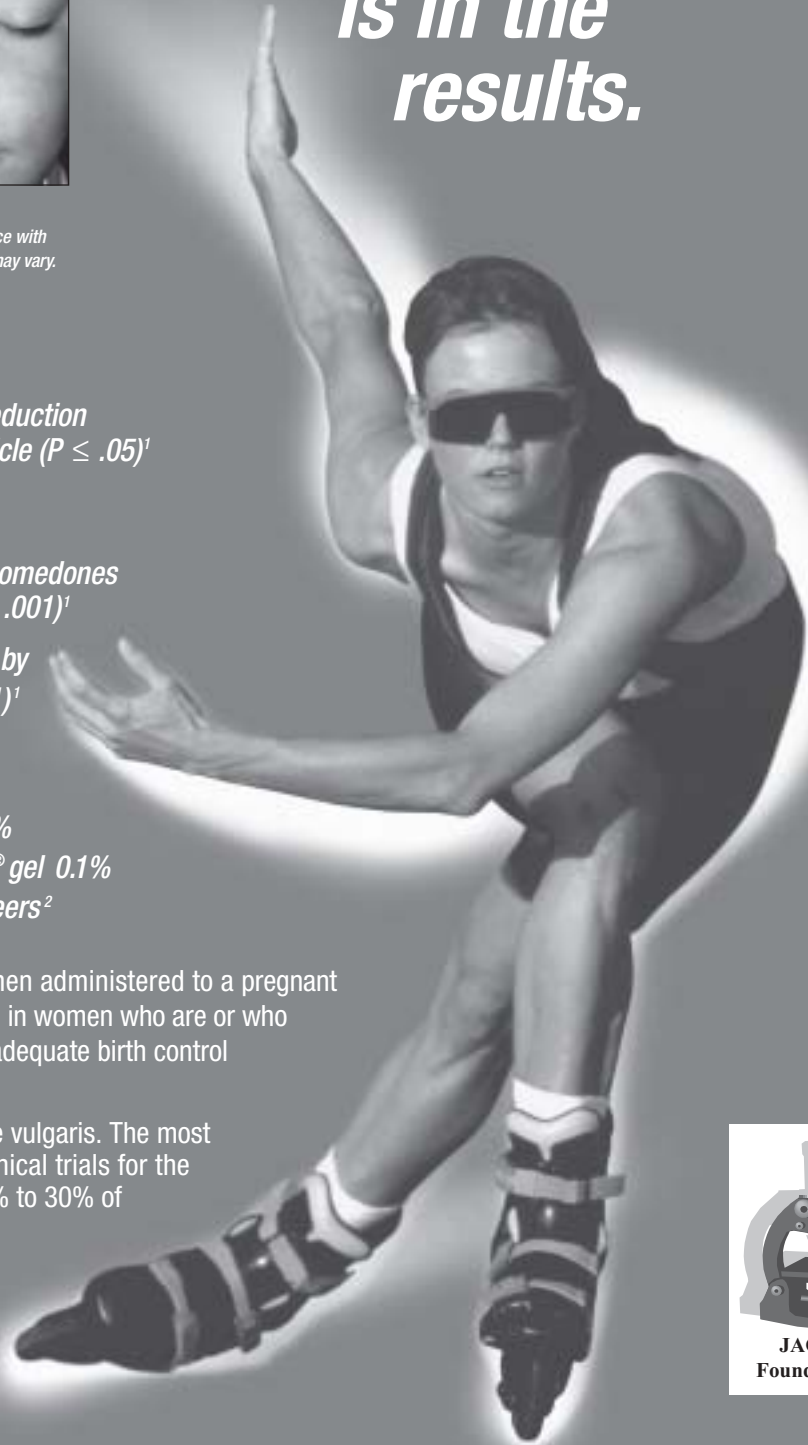
- Tolerability of TAZORAC® Cream 0.1% proven to be comparable to Differin® gel 0.1% in a 4-week study of healthy volunteers<sup>2</sup>

Because retinoids may cause fetal harm when administered to a pregnant woman, TAZORAC® Cream is contraindicated in women who are or who may become pregnant. Women should use adequate birth control measures when TAZORAC® Cream is used.

TAZORAC® Cream 0.1% is indicated for acne vulgaris. The most frequent adverse events reported during clinical trials for the treatment of acne vulgaris were seen in 10% to 30% of patients and included, in descending order, desquamation, dry skin, erythema, and burning sensation.

**TAZORAC®**  
(TAZAROTENE) 0.1%  
*cream*

Think **power**. Think **cream**.



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1. Data on file, Allergan, Inc. [TAZORAC® Cream vs vehicle in acne.]
  2. Data on file, Allergan, Inc. [Leyden data, TAZORAC® Cream vs Differin®.]
- Please see adjacent page for brief summary of prescribing information.

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Differin is a registered trademark owned by Galderma Laboratories, L.P.

**ALLERGAN**  
SKINCARE

# TAZORAC® (tazarotene) Cream, 0.1%

**BRIEF SUMMARY** (For full prescribing information, see package insert)

**INDICATIONS AND USAGE:** TAZORAC® (tazarotene) Cream 0.1% is indicated for the topical treatment of patients with acne vulgaris.

**CONTRAINDICATIONS:**

Retinoids may cause fetal harm when administered to a pregnant woman.

In rats, tazarotene 0.05% gel administered **topically** during gestation days 6 through 17 at 0.25 mg/kg/day resulted in reduced fetal body weights and reduced skeletal ossification. Rabbits dosed **topically** with 0.25 mg/kg/day tazarotene gel during gestation days 6 through 18 were noted with single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies. Systemic exposure (AUC<sub>0-24</sub>) to tazarotenic acid at topical doses of 0.25 mg/kg/day tazarotene in a gel formulation in rats and rabbits represented 4.0 and 44 times, respectively, the maximum AUC<sub>0-24</sub> in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area in a controlled pharmacokinetic study.

As with other retinoids, when tazarotene was given **orally** to experimental animals, developmental delays were seen in rats; and teratogenic effects and post-implantation loss were observed in rats and rabbits at doses producing 3.5 and 85 times, respectively, the maximum exposure (AUC<sub>0-24</sub>) seen in acne patients treated topically with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area in a controlled pharmacokinetic study.

In a study of the effect of oral tazarotene on fertility and early embryonic development in rats, decreased number of implantation sites, decreased litter size, decreased number of live fetuses, and decreased fetal body weights, all classic developmental effects of retinoids, were observed when female rats were administered 2 mg/kg/day from 15 days before mating through gestation day 7. A low incidence of retinoid-related malformations at that dose were reported to be related to treatment. That dose produced an AUC<sub>0-24</sub> that was 11 times that observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area.

Systemic exposure to tazarotenic acid is dependent upon the extent of the body surface area treated. IN PATIENTS TREATED TOPICALLY OVER SUFFICIENT BODY SURFACE AREA, EXPOSURE COULD BE IN THE SAME ORDER OF MAGNITUDE AS IN THESE ORALLY TREATED ANIMALS. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.

There were three reported pregnancies in patients who participated in the clinical trials on acne with tazarotene cream 0.1%. Two of the patients were found to have been treated with tazarotene cream and the other had been treated with vehicle. One of the patients who was treated with tazarotene cream elected to terminate the pregnancy. The other gave birth to an apparently normal, healthy child at 36 weeks gestation. Seven pregnant women who were inadvertently exposed to topical tazarotene during other clinical trials subsequently delivered healthy babies. As the exact timing and extent of exposure in relation to the gestation times are not certain, the significance of these findings is unknown.

TAZORAC® Cream is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued and the patient apprised of the potential hazard to the fetus. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for human chorionic gonadotropin (hCG) should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. (see also PRECAUTIONS: Pregnancy; Teratogenic Effects).

TAZORAC® Cream is contraindicated in individuals who have shown hypersensitivity to any of its components.

**WARNINGS:**

**Pregnancy Category X.** See CONTRAINDICATIONS section. Women of child-bearing potential should be warned of the potential risk and use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of child-bearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period.

**PRECAUTIONS:**

**General:** TAZORAC® Cream should be applied only to the affected areas. For external use only. Avoid contact with eyes, eyelids, and mouth. If contact with eyes occurs, rinse thoroughly with water.

Retinoids should not be used on eczematous skin, as they may cause severe irritation.

Because of heightened burning susceptibility, exposure to sunlight (including sunlamps) should be avoided unless deemed medically necessary, and in such cases, exposure should be minimized during the use of TAZORAC® Cream. Patients must be warned to use sunscreens (minimum SPF of 15) and protective clothing when using TAZORAC® Cream. Patients with sunburn should be advised not to use TAZORAC® Cream until fully recovered. Patients who may have considerable sun exposure due to their occupation and those patients with inherent sensitivity to sunlight should exercise particular caution when using TAZORAC® Cream and ensure that the precautions outlined in the Information for Patients subsection of the full package insert are observed.

TAZORAC® Cream should be administered with caution if the patient is also taking drugs known to be photosensitizers (e.g., thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Some individuals may experience excessive pruritus, burning, skin redness or peeling. If these effects occur, the medication should either be discontinued until the integrity of the skin is restored, or the dosing should be reduced to an interval the patient can tolerate. However, efficacy at reduced frequency of application has not been established. Weather extremes, such as wind or cold, may be more irritating to patients using TAZORAC® Cream.

**Drug Interactions:** Concomitant dermatologic medications and cosmetics that have a strong drying effect should be avoided. It is also advisable to "rest" a patient's skin until the effects of such preparations subside before use of TAZORAC® Cream is begun.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

A long term study of tazarotene following oral administration of 0.025, 0.050, and 0.125 mg/kg/day to

rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to 2.0 times the maximum AUC<sub>0-24</sub> seen in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area in a controlled pharmacokinetic study. In evaluation of photo co-carcinogenicity, median time to onset of tumors was decreased, and the number of tumors increased in hairless mice following chronic topical dosing with intercurrent exposure to ultraviolet radiation at tazarotene concentrations of 0.001%, 0.005%, and 0.01% in a gel formulation for up to 40 weeks.

A long-term topical application study of up to 0.1% tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.05, 0.125, 0.25, and 1.0 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermal irritation) revealed no apparent carcinogenic effects when compared to vehicle control animals; untreated control animals were not completely evaluated. Systemic exposure (AUC<sub>0-24</sub>) at the highest dose was 13 times the maximum AUC<sub>0-24</sub> seen in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area in a controlled pharmacokinetic study.

Tazarotene was found to be non-mutagenic in the Ames assays using Salmonella and *E. coli* and did not produce structural chromosomal aberrations in a human lymphocyte assay. Tazarotene was also non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-clastogenic in the *in vivo* mouse micronucleus test.

No impairment of fertility occurred in rats when male animals were treated for 70 days prior to mating and female animals were treated for 14 days prior to mating and continuing through gestation and lactation with topical doses of tazarotene gel up to 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum AUC<sub>0-24</sub> observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area in a controlled pharmacokinetic study.

No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of up to 1.0 mg/kg/day tazarotene. That dose produced an AUC<sub>0-24</sub> that was 6.3 times the maximum AUC<sub>0-24</sub> observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area.

No effect on parameters of mating performance or fertility was observed in female rats treated for 15 days prior to mating and continuing through day 7 of gestation with oral doses of tazarotene up to 2.0 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental effects at that dose (see CONTRAINDICATIONS). That dose produced an AUC<sub>0-24</sub> that was 11 times the maximum AUC<sub>0-24</sub> observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area.

Reproductive capabilities of F1 animals, including F2 survival and development, were not affected by topical administration of tazarotene gel to female F0 parental rats from gestation day 16 through lactation day 20 at the maximum tolerated dose of 0.125 mg/kg/day. Based on data from another study, the systemic drug exposure in the rat would be equivalent to 2.0 times the maximum AUC<sub>0-24</sub> observed in acne patients treated with 0.1% tazarotene cream at 2 mg/cm<sup>2</sup> over 15% body surface area.

**Pregnancy: Teratogenic Effects: Pregnancy Category X:**

See CONTRAINDICATIONS section. Women of child-bearing potential should use adequate birth-control measures when TAZORAC® Cream is used. The possibility that a woman of childbearing potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy test having a sensitivity down to at least 50 mIU/mL for hCG should be obtained within 2 weeks prior to TAZORAC® Cream therapy, which should begin during a normal menstrual period. There are no adequate and well-controlled studies in pregnant women. Although there may be less systemic exposure in the treatment of acne of the face alone due to less surface area for application, tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.

**Nursing mothers:**

After single topical doses of <sup>14</sup>C-tazarotene gel to the skin of lactating rats, radioactivity was detected in milk, suggesting that there would be transfer of drug-related material to the offspring via milk. It is not known whether this drug is excreted in human milk. Caution should be exercised when tazarotene is administered to a nursing woman.

**Pediatric Use:**

The safety and efficacy of tazarotene cream have not been established in patients with acne under the age of 12 years.

**Geriatric Use:**

Tazarotene cream for the treatment of acne has not been clinically tested in persons 65 years of age or older.

**ADVERSE REACTIONS:**

In human dermal safety studies, tazarotene 0.05% and 0.1% creams did not induce allergic contact sensitization, phototoxicity, or photoallergy.

The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne, occurring in 10-30% of patients, in descending order included desquamation, dry skin, erythema, and burning sensation. Events occurring in 1 to 5% of patients included pruritus, irritation, face pain, and stinging.

**OVERDOSAGE:**

Excessive topical use of TAZORAC® Cream 0.1% may lead to marked redness, peeling, or discomfort (see PRECAUTIONS: General).

TAZORAC® Cream 0.1% is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored and appropriate supportive measures should be administered as necessary.

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# Porokeratosis of Mibelli Occurring After Allogeneic Bone Marrow Transplant: A Case Report and Review of the Literature

Risa Gorin, DO, Charles A Gropper, MD, Cindy F Hoffman, DO

## Abstract

*Porokeratosis is a disorder of keratinization characterized histologically by the presence of a cornoid lamella. While the association of porokeratosis and immunosuppression has been reported, few cases have been documented after bone marrow transplant. A case of a 19 year-old African American male that developed Porokeratosis of Mibelli after an allogeneic bone marrow transplant for acute myelogenous leukemia is presented. In addition, the salient clinical and histologic features of porokeratosis, its associations with immunosuppression, premalignant potential, clinical course and treatment options are reviewed.*

## Case Report

N.C. is a 19 year-old African American male who presented to our dermatology clinic with a seven-year history of a persistent rash. The lesions began on his proximal extremities and increased in number and size over time. It was occasionally pruritic and unresponsive to treatment with super-high potency topical steroids. He stated that the rash began approximately one year after a bone marrow transplant and that he was not taking any immunosuppressants when the rash started.

His past medical history was significant for an allogeneic bone marrow transplant at the age of 9 for acute myelogenous leukemia. The patient reports that he also received chemotherapy and radiation therapy to the neck for his leukemia prior to the bone marrow transplant. He denied any other medical problems, was taking no medications, and denied drug allergies. His family history was negative for chronic skin conditions. He was a student and denied tobacco, illicit drugs, and alcohol.

A comprehensive cutaneous examination revealed four discrete annular plaques with central clearing and a peripheral keratotic ridge, ranging in size from 1.5 to 3.0 cm, on the extremities (Figure 1 and Figure 2). Four similar, but smaller, lesions were identified on the shaft of the penis and two hyperpigmented prurigo-like nodules were on his abdomen and right hand. There were no oral lesions.

The clinical differential diagnosis at that time included chronic graft versus host, lichen planus, porokeratosis of Mibelli, disseminated superficial porokeratosis, and granuloma annulare. A 3-mm punch biopsy was performed from his left knee lesion. Histologically, within the cornified layer there was an elongated column of parakeratosis coming off the epidermis at a forty-five degree angle. Underneath the column of parakeratosis,



**Figure 1 and Figure 2. Well defined annular plaques with central clearing and a peripheral keratotic ridge on the right shoulder and left knee, respectively.**



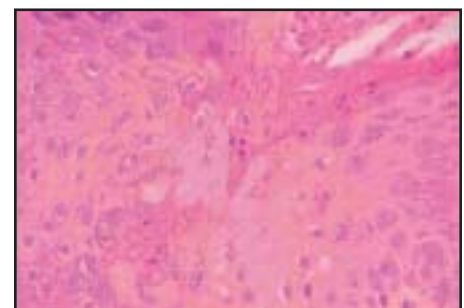
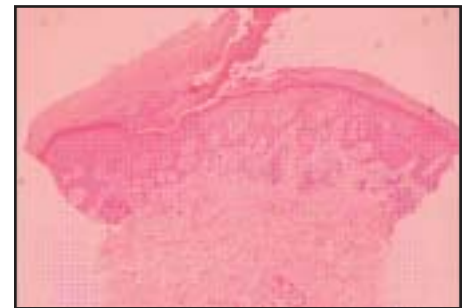
there was an absent granular layer and, focally, dyskeratotic and large keratinocytes with hyperchromatic nuclei. The epidermis showed uniform, mild psoriasiform hyperplasia. Within the dermis there was a superficial perivascular lymphohistiocytic infiltrate. (Figures 3 to 5) These findings were considered characteristic for porokeratosis of Mibelli.

## Comment

Porokeratosis is a disorder of keratinization, which is characterized histologically by the presence of a cornoid lamella—a thin column of closely stacked, parakeratotic cells extending through the stratum corneum<sup>(1)</sup>. Mibelli first described Porokeratosis in 1893<sup>(2)</sup>. Today, five clinical variants are recognized: classic porokeratosis of Mibelli, disseminated superficial porokeratosis (DSP) and dis-



**Figure 3 (H & E original magnification x 20) and Figure 4 (H & E original magnification x 40) demonstrating the elongated column of parakeratosis, the cornoid lamella, coming off the epidermis at an angle.**



**Figure 5 (H&E original magnification x 100). Underneath the column of parakeratosis, there is an absent granular layer and dyskeratotic and large keratinocytes with hyperchromatic nuclei.**

seminated superficial actinic porokeratosis (DSAP), porokeratosis palmaris et plantaris disseminata (PPPD), linear porokeratosis, and punctate porokeratosis. Different clinical variants have been reported to coexist in an individual patient<sup>(3)</sup>.

Classic lesions of porokeratosis of Mibelli start as small, brownish, keratotic papules, which slowly enlarge forming irregular, annular plaques with a well-demarcated raised hyperkeratotic border. The center of the lesion is usually atrophic, hairless, hypo- or hyperpigmented and can range in size from a few millimeters to several centimeters in diameter. Usually, only a few lesions are present and they can be present anywhere, but are typically found on the acral areas of the extremities, thighs, and perigenital region. Lesions can spread by koebnerization<sup>(4)</sup>.

The onset of porokeratosis of Mibelli is during childhood and lesions slowly enlarge over time. Lesions are usually asymptomatic. Family studies suggest an autosomal dominant mode of inheritance. Males are more often affected than females<sup>(4)</sup>.

The most common form of porokeratosis, DSP, is a more generalized process involving mainly the extremities in a symmetric, bilateral fashion. The palms, soles, mucous membranes, inguinal folds, and axillae are spared. In half of the cases, lesions are restricted to sun-exposed areas (DSAP). Clinically, lesions of DSP and DSAP are small, superficial, numerous, and appear in crops. Early lesions are small, keratotic papules, often with a central dell, measuring 1 to 3 mm in diameter. They may be erythematous, pigmented, or flesh colored. Lesions enlarge to form superficial, ring-like lesions with a slightly atrophic center surrounded by a very discrete ridge topped by a barely visible furrow. Koebner phenomenon is not observed<sup>(5)</sup>.

DSP and DSAP occur equally in both sexes. They usually start in the third and fourth decades and are slowly progressive over years. Genetic studies show that DSP and DSAP are inherited in an autosomal dominant mode with a reduced penetrance at a young age<sup>(6)</sup>. DSAP is more often observed in geographic areas with high sun exposure, and is extremely rare in blacks<sup>(5,7,8)</sup>. Prolonged exposure to artificial UV light<sup>(9)</sup>, photochemotherapy<sup>(10)</sup>, and phototherapy for psoriasis<sup>(11)</sup> can exacerbate lesions.

Lesions of PPPD are superficial, small, relatively uniform, and outlined by a distinctive peripheral ridge of no more than 1 mm in height. Palmar and plantar lesions are generally more hyperkeratotic with a

more pronounced longitudinal furrow. Clinically, lesions first arise on the palms and soles and spread in large numbers over the extremities and trunk, including non-sun exposed areas and mucous membranes. Lesions may be pruritic. The onset of PPPD is usually during adolescence and early adulthood. It is inherited in an autosomal dominant mode and affects males twice as often as females<sup>(4)</sup>.

Linear porokeratosis presents in a distinctly unilateral, linear manner. Clinically, the lesions are identical to those of the Mibelli type, including lichenoid papules, small annular lesions, hyperkeratotic plaques with central atrophy, and the characteristic peripheral ridge. However, lesions are grouped and linearly arranged on the extremities, more commonly on the distal aspects. They may even be in a zosteriform distribution<sup>(12)</sup>. Onset is usually in infancy and childhood, but no definite inheritance pattern has been established<sup>(4)</sup>. Lesions of linear porokeratosis have been reported to have a higher incidence of malignant transformation compared to other types of porokeratosis<sup>(13)</sup>.

Punctate porokeratosis is usually associated with either linear porokeratosis or classic Mibelli. Multiple, minute, discrete, punctate, hyperkeratotic, lesions surrounded by a thin, raised margin are present on the palms and soles. Lesions may coalesce to form plaques or may be linearly arranged.

The etiology of porokeratosis is unknown. Mibelli termed the disorder porokeratosis for its presumed origin in the acrosyringeal portion of eccrine sweat ducts, a belief supported by several authors<sup>(2)</sup>. It is now well accepted that cornoid lamellae emanate not only from eccrine sweat ducts, but also from infundibula of hair follicles, and from epidermis proper<sup>(1)</sup>.

To some investigators, the cornoid lamella represents a defect in cornification. Reed and Leone proposed that porokeratosis of Mibelli could be related to mutant cellular "clones" of epithelial cells in the epidermis, and the cornoid lamella was a marker for the boundary between the abnormal clonal population and the normal epithelium<sup>(14)</sup>. This theory assumes that changes in the dermis beneath porokeratotic lesions are secondary to those in the epidermis and not part of the causal mechanism<sup>(14,15)</sup>. Additionally, altered Langerhans cell surface markers in lesional DSAP skin in immunosuppressed subjects was found by Manganoni, et al. suggesting that altered immune surveillance by epidermal Langerhans cells may allow the development of an abnormal clone of epidermal keratinocytes<sup>(16)</sup>.

In contradiction to Reed and Leone's hypothesis, there are reports suggesting that dermal injury could be an initiating factor in the pathogenesis of porokeratosis<sup>(1)</sup>. Wade and Ackerman have hypothesized that fibrotic scarring and inflammation in the papillary dermis are probable causal mechanisms for lamellation and may disorder epithelial metabolism. Furthermore, they state that other diseases of the skin characterized by parakeratosis (e.g. solar keratosis, psoriasis, and pale cell acanthoma) result from abnormalities of the papillary dermis that are subsequently manifested in the epidermis<sup>(1)</sup>.

Actinic damage may play a role in the development of porokeratosis. This has been well studied in DSAP, and a number of patients receiving topical<sup>(17)</sup> and systemic<sup>(10)</sup> PUVA therapy have developed DSAP. In addition, under experimental conditions, UV light exposure has induced DSAP-like lesions<sup>(9)</sup>.

A hypothetical infectious agent has been suggested to be the etiology for the development of porokeratosis in transplant recipients<sup>(18,19)</sup>. However, no report on transmissibility of porokeratosis has been published<sup>(7,20)</sup>.

Specimens for biopsy should be taken from the peripheral, raised, hyperkeratotic ridge. On histologic examination, the ridge then shows a keratin-filled invagination of the epidermis. In the plaque type of porokeratosis, the invagination extends deeply downward at an angle, the apex of which points away from the central portion of the lesion. In the center of this keratin-filled invagination rises a parakeratotic column, the so-called cornoid lamella, representing the most characteristic feature of porokeratosis of Mibelli. Within the parakeratotic column, the horny cells appear homogeneous and possess pyknotic nuclei. In the epidermis beneath the parakeratotic column, the keratinocytes are irregularly arranged and have pyknotic nuclei with perinuclear edema. Usually an absent or decreased granular layer is found at the site at which the parakeratotic column arises.

The epidermis overlying the central portion of a lesion of porokeratosis may be either flattened or normal in thickness or rarely, acanthotic. A nonspecific perivascular infiltrate of chronic inflammatory cells is present in the dermis.

The histologic changes in the other forms of porokeratosis are similar to those seen in the plaque type but less pronounced, the central invagination being rather shallow, especially in DSAP. Additionally, DSAP displays epidermal atrophy and solar elastosis.

Acquired immunodeficiency is frequently found as a prelude to the development of porokeratosis and can account for half of new cases<sup>(15,21)</sup>. Organ transplantation is the most common immune deficiency favoring the development of porokeratosis<sup>(22)</sup>. Many reports describe exacerbation of lesions associated with immune depression<sup>(14)</sup>, and others, the complete remission of porokeratosis after withdrawing immunosuppressants<sup>(14, 23)</sup>. How immune suppression can induce the genesis of porokeratosis is not known. However, clinical and histopathologic findings revealed that the nature of the disease is essentially the same in both the immunosuppressed and nonimmunosuppressed patients<sup>(15)</sup>.

The reported incidence of porokeratosis occurring after organ transplantation in the different published series varies greatly from 0.34% to 11%<sup>(23)</sup>. Over 60 patients with various clinical forms of porokeratosis occurring after organ transplant have been reported including kidney, heart, bone marrow<sup>(-5)</sup>, lung, and liver grafts. The majority, however, had the disseminated superficial form of porokeratosis<sup>(7,20,22)</sup>.

Although the pathogenesis of porokeratosis is unknown, it was for many years viewed as a benign entity. Despite several reports of malignancy arising in lesions of porokeratosis, it was not until 1968 that serious consideration was given to the premalignant nature of this disorder<sup>(25,26)</sup>. The potential for malignancy has not been well defined, and the risk of malignant transformation remains unknown. Early reports of malignancy arising in lesions of porokeratosis strongly correlated with a history of radiation treatment<sup>(25)</sup>.

In 1996, Sasson and Krain<sup>(25)</sup> reviewed the English literature from 1964-1994 and identified 281 cases of porokeratosis, 21 (7.5%) of which had an associated malignancy that developed within a lesion of porokeratosis. They found that older patients and those with longstanding disease were found to be at increased risk for the development of malignancy. Malignant lesions tended to occur on the extremities, with only 2 patients displaying malignancies on the trunk. They found that out of the 21 malignancies, eight arose in linear porokeratosis. This was consistent with prior findings of an increased malignant potential in the linear form<sup>(13)</sup>. However, in contrast to previous reports, only 2 patients had a history of irradiation. Additionally, no cases were associated with iatrogenic immune suppression.

Others have reported similar rates of malignant degeneration<sup>(27)</sup>, with the most

commonly reported malignant lesions being Bowen's disease, squamous cell carcinoma, and rarely, basal cell carcinoma<sup>(25,27)</sup>. Rarely, however, do these neoplasms metastasize. However, recently, a case of disseminated porokeratosis with fatal metastatic squamous cell carcinoma has been reported<sup>(28)</sup>.

To support the belief that porokeratosis represents a premalignant condition, cytologic and ultrastructural studies were performed on lesional skin. Cytologically, it has been demonstrated that fibroblasts from lesional skin show chromosomal abnormalities as well as clonal populations of cytogenetically abnormal cells<sup>(29)</sup>. These changes were not present in unaffected skin. Ultrastructural studies of lesional keratinocytes reveal abnormal keratinization patterns<sup>(30)</sup>. Immunohistochemical staining patterns of keratinocytes below the cornoid lamella are similar to those observed in squamous cell carcinoma, while centrally located cells stain similar to actinic keratoses<sup>(31)</sup>. This failure of normal keratinocyte differentiation may indicate a premalignant state. In addition, overexpression of p53 has been found in some biopsy samples of DSAP with and without malignant degeneration<sup>(32)</sup>. However, this overexpression of p53 and its potential relationship to the premalignant nature of porokeratosis has yet to be elucidated.

When considering treatment options, the optimal procedure must be selected depending on the lesion's size and location, functional and aesthetic requirements, and the general condition of the patient. Lesions can recur with many therapeutic modalities. Circumscribed lesions of porokeratosis of Mibelli or linear porokeratosis may be excised or destroyed by cryotherapy, electrodesiccation, dermabrasion, CO2 laser<sup>(33)</sup> or 585 pulsed dye laser<sup>(34)</sup>. Lubrication usually improves the symptoms in superficial forms of porokeratosis, as does keratolytic treatment of hyperkeratotic lesions. Other topical therapies reported with varying success include topical 5-fluorouracil<sup>(35)</sup>, retinoids, and imiquimod<sup>(36)</sup>. The use of oral retinoids has yielded conflicting results<sup>(37)</sup>. Cytologic atypia disappeared with retinoid therapy, thus, they might have an inhibitory effect on cutaneous carcinogenesis in porokeratotic lesions<sup>(4)</sup>. However, one must be aware that relapses usually follow several weeks or months after discontinuation of retinoid therapy.

Lastly, all therapeutic measures that might increase the malignant potential of porokeratosis (radiation, immunosuppression, and excessive UV exposure) should be avoided. And, in spite of a poorly defined pathogenesis, porokeratosis dis-

plays a potential for malignancy. Therefore, careful observation is warranted.

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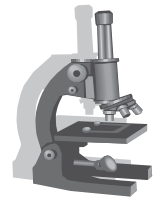
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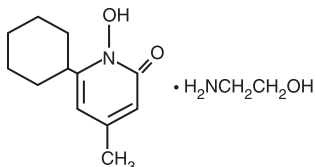
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**CLINICAL PHARMACOLOGY:** Ciclopirox is a broad-spectrum, antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts, and *Malassezia furfur*. Ciclopirox exhibits fungicidal activity *in vitro* against isolates of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Microsporum canis*, and *Candida albicans*.

Pharmacokinetic studies in men with radiolabeled ciclopirox solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically to 750 cm<sup>2</sup> on the back followed by occlusion for 6 hours. The biological half-life was 1.7 hours and excretion occurred via the kidney. Two days after application only 0.01% of the dose applied could be found in the urine. Fecal excretion was negligible. Autoradiographic studies with human cadaver skin showed that ciclopirox penetrates into the hair and through the epidermis and hair follicles into the sebaceous glands and dermis, while a portion of the drug remains in the stratum corneum.

*In vitro* penetration studies in frozen or fresh excised human cadaver and pig skin indicated that the penetration of LOPROX Topical Suspension is equivalent to that of Loprox<sup>®</sup> (ciclopirox) Cream 0.77%. Therapeutic equivalence of cream and suspension formulations also was indicated by studies of experimentally induced guinea pig and human trichophytosis.

**INDICATIONS AND USAGE:** LOPROX Topical Suspension is indicated for the topical treatment of the following dermal infections: tinea pedis, tinea cruris and tinea corporis due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis*; cutaneous candidiasis (moniliasis) due to *Candida albicans*; and tinea (pityriasis) versicolor due to *Malassezia furfur*.

**CONTRAINDICATIONS:** LOPROX Topical Suspension is contraindicated in individuals who have shown hypersensitivity to any of its components.

**WARNINGS: General:** LOPROX Topical Suspension is not for ophthalmic use.

**PRECAUTIONS:** If a reaction suggesting sensitivity or chemical irritation should occur with the use of LOPROX Topical Suspension, treatment should be discontinued and appropriate therapy instituted.

**Reference:**

1. Data on file, Medicis Pharmaceutical Corporation

**Information for Patients:** The patient should be told to:

1. Use the medication for the full treatment time even though signs/symptoms may have improved and notify the physician if there is no improvement after four weeks.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** A carcinogenicity study in female mice dosed cutaneously twice per week for 50 weeks followed by a 6-month drug-free observation period prior to necropsy revealed no evidence of tumors at the application site. The following *in vitro* and *in vivo* genotoxicity tests have been conducted with ciclopirox olamine: studies to evaluate gene mutation in the Ames *Salmonella*/Mammalian Microsome Assay (negative) and Yeast Saccharomyces *Cerevisiae* Assay (negative) and studies to evaluate chromosome aberrations *in vivo* in the Mouse Dominant Lethal Assay and in the Mouse Micronucleus Assay at 500 mg/kg (negative). The following battery of *in vitro* genotoxicity tests were conducted with ciclopirox: a chromosome aberration assay in V79 Chinese Hamster Cells, with and without metabolic activation (positive); a gene mutation assay in the HGPRT - test with V79 Chinese Hamster Cells (negative) and a primary DNA damage assay (i.e., unscheduled DNA Synthesis Assay in A549 Human Cells (negative)). An *in vitro* Cell Transformation Assay in BALB/C3T3 Cells was negative for cell transformation. In an *in vivo* Chinese Hamster Bone Marrow Cytogenetic Assay, ciclopirox was negative for chromosome aberrations at 5000 mg/kg.

**Pregnancy Category B:** Reproduction studies have been performed in the mouse, rat, rabbit, and monkey, via various routes of administration, at doses 10 times or more the topical human dose and have revealed no significant evidence of impaired fertility or harm to the fetus due to ciclopirox. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when LOPROX Topical Suspension is administered to a nursing woman.

**Pediatric Use:** Safety and effectiveness in pediatric patients below the age of 10 years have not been established.

**ADVERSE REACTIONS:** In the controlled clinical trial with 89 patients using LOPROX Topical Suspension and 89 patients using the vehicle, the incidence of adverse reactions was low. Those considered possibly related to treatment or occurring in more than one patient were pruritus, which occurred in two patients using ciclopirox suspension and one patient using the suspension vehicle, and burning, which occurred in one patient using ciclopirox suspension.

**DOSAGE AND ADMINISTRATION:** Gently massage LOPROX Topical Suspension into the affected and surrounding skin areas twice daily, in the morning and evening. Clinical improvement with relief of pruritus and other symptoms usually occurs within the first week of treatment. If a patient shows no clinical improvement after four weeks of treatment with LOPROX Topical Suspension the diagnosis should be redetermined. Patients with tinea versicolor usually exhibit clinical and mycological clearing after two weeks of treatment.

**HOW SUPPLIED:** LOPROX<sup>®</sup> (ciclopirox) Topical Suspension 0.77% is supplied in 30 mL bottles (NDC 99207-022-30), 60 mL bottles (NDC 99207-022-60).

**Bottle space provided to allow for vigorous shaking before each use.**

Store between 5° and 25°C (41° and 77°F).

US Patent Pending

Prescribing Information as of May 2002

**Manufactured for:**

MEDICIS, The Dermatology Company

Scottsdale, AZ 85258

by: Patheon, Inc.

Mississauga, Ontario L5N 7K9 CANADA

Made in Canada

REG TM MEDICIS

MEDICIS, The Dermatology Company<sup>®</sup>



# Pharmacotherapy Review: Topical Tazarotene

## A Composite Review of Clinical & Research Experience With Focus on Optimal Use and Safety

James Q. Del Rosso, D.O., FAOCD

### Abstract

*Tazarotene is a synthetic retinoid compound with unique properties, approved as topical therapy for acne vulgaris, psoriasis and photoaging. Efficacy and safety have been confirmed in multiple, well-designed controlled studies. Initial availability in a gel formulation proved to be clinically effective, but was limited by a high incidence of irritation. Additional blinded, controlled studies have demonstrated high efficacy with every other night application of tazarotene 0.1% gel for facial acne vulgaris, with efficacy and tolerance comparable to other topical retinoids applied nightly. Studies with a newer tazarotene 0.1% cream formulation applied daily confirm favorable efficacy and patient tolerance in both acne vulgaris and photoaging, including short term and long term trials for the latter application. For therapy of plaque psoriasis, topical tazarotene has been shown to be effective, with optimal results achieved in combination with topical corticosteroids, including mid, high and super-potency agents; efficacy superior to other topical therapy approaches including calcipotriene has been documented. Steroid-enhancing and sparing effects with improved maintenance of disease control and a reduction of topical steroid-induced cutaneous atrophy have been documented with topical tazarotene use. Topical tazarotene has also been used effectively and safely in patients of various ethnicities, including African-American patients. Pharmacokinetic studies have confirmed limited systemic absorption of tazarotene after topical application. The efficacy, safety data and experience related to topical tazarotene use based on review of studied applications, with special emphasis on acne treatment, are presented. Suggestions for optimal use of tazarotene are outlined.*

### Cellular Mechanisms Modulated by Tazarotene

Topical tazarotene is a “precursor” compound, metabolized rapidly by esterase hydrolysis to its active retinoid metabolite, tazarotenic acid, after cutaneous application.<sup>1</sup> With increased understanding of cellular mechanisms involved in differentiation and inflammation, the effects of topical retinoids, including tazarotene, extend beyond their long-established comedolytic activity.

Tazarotenic acid is believed to modulate its therapeutic effects in skin predominantly via high affinity binding to retinoic acid receptor-gamma (RAR gamma); binding also occurs to RAR-beta and weakly to RAR-alpha, but not to retinoid X receptors (RXRs).<sup>1,3</sup> The impact of RAR binding by tazarotenic acid corresponds with the modulation and expression of retinoid-responsive genes regulating cell differentiation, proliferation and inflammatory pathways.<sup>1,3</sup> Several observed biologic effects appear to relate to the mechanisms of action of tazarotene for treatment of acne, psoriasis and/or photo-damage.<sup>1,3,8</sup> These include:

- downregulated aberrant expression of keratinocyte transglutaminase I (Tgase I)
- downregulated expression of epidermal growth factor receptor
- decreased markers of inflammation such as migration inhibitory factor-related protein (MRP-8)
- reduced expression of hyperproliferative

keratins (K6, K16) that are increased during early comedogenesis

- suppression of the AP-1 transcription factor pathway

Topical retinoids have also been shown to reduce expression and binding of toll-like receptors (ie. TLR-2) involved in the proinflammatory cytokine production and stimulation of inflammatory pathways induced by *Propionibacterium acnes*.<sup>9-11</sup> In addition, by reducing comedogenesis, topical retinoids such as tazarotene, prevent the formation of a follicular microclimate required for proliferation of *P. acnes* organisms.<sup>12</sup> Topical retinoids also suppress activation of the AP-1 transcription factor pathway involved in the regulation of matrix metalloproteinase genes.<sup>1,11,13</sup> A rational model based on *in vivo* human studies supports this pathway as a component of acne inflammation and scarring.<sup>11</sup> AP-1 protein is also overexpressed in a variety of hyperproliferative and inflammatory disorders.<sup>1</sup>

### Pharmacokinetics, Pharmacology and Toxicology of Tazarotene

**Pharmacokinetics.** The systemic absorption of tazarotene is minimal due to rapid conversion to tazarotenic acid. The half-life of tazarotene is 2 – 18 minutes.<sup>1</sup> Maximum concentration of tazarotenic acid in systemic circulation is noted at 9 hours after application with up to 5 % total systemic absorption of applied drug noted after application to normal skin;

<1% of radiolabeled tazarotene is absorbed within 10 hours of application on unoccluded psoriatic skin and <6 % is absorbed within 10 hours on occluded normal skin.<sup>3,14,15,16,17</sup> Tazarotenic acid (free acid form) is rapidly deactivated to inactive sulfone and sulfoxides metabolites that are excreted in the urine; the elimination half-life of tazarotenic acid is 1 – 2 hours and the terminal half-life is approximately 18 hours.<sup>1,3,14,18</sup>

**Toxicology.** During preclinical toxicology evaluation, a battery of tests revealed that tazarotene was nonmutagenic, non-carcinogenic and without evidence of chromosomal effects. As with other retinoids, high dose oral administration of tazarotene induced teratogenicity, however, teratogenicity was not observed after high dose topical application of tazarotene in both rabbit and rat models.<sup>1,3,7,15</sup>

No clinically significant systemic, ophthalmologic, hematologic abnormalities or changes in serum chemistry parameters were observed in association with topical application of tazarotene.<sup>3,15</sup>

### Impact of Repeated Applications of Tazarotene

**Plasma Concentrations of Tazarotenic Acid.** Plasma concentration versus time profiles were evaluated following single and repeated applications of tazarotene 0.1% cream applied once daily for 28 days in female patients with moderate-to-severe facial acne.<sup>19</sup> Applications were made to the face only or to an exagger-

ated body surface area (15% BSA) involving face, upper trunk, shoulders and/or neck. Multiple sequential plasma concentrations were completed throughout the study inclusive of the 72 hour period after the first and last applications and over 24 hours after dosing on days 8, 15 and 22. In both study groups, maximal plasma concentration was noted on day 15, suggesting that continued accumulation of drug within the plasma compartment does not occur with repeated topical application of tazarotene. In study patients completing only repeated facial applications, tazarotenic acid plasma concentrations were very low (~ 0.1 ng/ml). In the study group applying drug to the expanded body surface area, plasma concentrations of tazarotenic acid were at the low end of the range of concentrations of endogenous tretinoin and its metabolites, oxoisotretinoin and isotretinoin (1 – 4 ng/ml), with the total cumulative retinoid concentration reported to be up to 8 ng/ml. As a comparison, the plasma concentration of isotretinoin that may be reached during a course of oral therapy for severe nodulocystic is >1000 ng/ml.<sup>20</sup>

Other studies have evaluated plasma concentrations of tazarotenic acid after application of tazarotene 0.05% and 0.1% gel, which range from 0.06 – 0.13 ng/ml; repeated application once daily over 28 days in female patients with facial acne reported a plasma concentration range of 0.136 + 0.107 ng/ml after the last drug application.<sup>21,22</sup>

These concentrations compare favorably to the reported plasma concentrations of endogenous tretinoin and its metabolites.<sup>23</sup>

**Relationship to Teratogenicity Risk.** Unlike other available prescription topical retinoids which are FDA-approved for treatment of photoaging and/or acne vulgaris and are classified as pregnancy category C, tazarotene is classified as pregnancy category X as it is the only topical retinoid also FDA-approved for treatment of psoriasis.<sup>3</sup> The categorization of tazarotene in pregnancy category X is based on precaution due to anticipated application to an extensive body surface area in some psoriasis patients and is not related to any cases of documented teratogenicity associated with topical tazarotene use in humans.<sup>3,24-26</sup> Pharmacovigilance has not detected cases of teratogenicity associated with inadvertent use of topical tazarotene in pregnant female patients.<sup>3,25,26</sup> Post treatment tazarotene/tazarotenic acid retinoid plasma levels are comparable to endogenous retinoid levels and levels achieved by tretinoin or adapalene after topical use, all of which are dramatically lower than plasma levels detected after use of

oral isotretinoin which produces 100-fold higher plasma retinoid concentrations than topical retinoid application.<sup>25</sup> It is recommended that practitioners exercise a cautious approach and avoid prescribing any topical retinoid to female patients during pregnancy.<sup>3</sup>

## Use of Tazarotene and Combination Therapy for Psoriasis

As psoriasis therapies, such as topical corticosteroids, and topical tazarotene are commonly used in combination for treatment of psoriasis, the impact of compatibility with tazarotene and the effect of tazarotene on corticosteroid-induced cutaneous atrophy are of clinical significance.

**Topical Corticosteroid-Induced Skin Atrophy.** A 4 week trial evaluated the cutaneous atrophogenic effect of diflorasone diacetate 0.05% ointment applied alone daily on 6 days per week to forearm skin in 24 human adult volunteers versus the effect of combination treatment with tazarotene 0.1% gel also applied daily on 6 days per week.<sup>27</sup> Tazarotene 0.1% gel alone increased mean epidermal thickness by 62% compared to 20% with placebo vehicle. Application of diflorasone diacetate 0.05% ointment alone reduced mean epidermal thickness by 43%. Statistically significant reduction in corticosteroid-induced atrophy was noted with the combination regimen; topical tazarotene reduced the epidermal atrophy associated with diflorasone diacetate use by 37% as compared to application of the corticosteroid alone.

**Compatibility with Other Psoriasis Therapies.** A two-week *in vitro* stability evaluation demonstrated good stability of all compounds when tazarotene was combined with equal quantities of several corticosteroid formulations including mometasone furoate 0.1% cream, fluocinonide 0.05% ointment and cream, betamethasone 0.05% cream and lotion, clobetasol dipropionate 0.05% ointment, cream and scalp solution and diflorasone diacetate 0.05 % ointment.<sup>28</sup> In a large trial of 300 patients, combination therapy regimens with a mid- or high potency topical corticosteroid applied in the morning and tazarotene gel applied in the evening have been shown to be effective, and also minimize associated skin irritation.<sup>29,30</sup> The parameters evaluating mean time to achieve >50% improvement, overall success at study end-point (12 weeks), clinical signs of psoriasis and local tolerability reactions responded more favorably in the groups utilizing topical corticosteroid-tazarotene regimens than with tazarotene monotherapy. Maintenance regimens utilizing topical tazarotene, evaluated over a

five month study phase to assess potential “steroid rebound” and exacerbations, have also shown that topical tazarotene enhances the ability to sustain control of psoriasis.<sup>31</sup>

Adjunctive use of fluticasone 0.05% ointment in the evening along with tazarotene 0.1% gel in the morning was shown in 12 week study to provide superior global improvement scores and a greater decrease in erythema and scaling than tazarotene monotherapy; the use of twice daily fluticasone offered little to no additional benefit over once daily usage.<sup>32</sup> Enhanced efficacy and favorable tolerance were also confirmed in studies evaluating the use of tazarotene gel formulations in combination with phototherapy using broad-band UVB, narrow band UVB and PUVA therapy.<sup>29</sup> Topical tazarotene has also been shown to be stable in the presence of calcipotriene.<sup>28</sup>

“Switch medication analysis” involving a change in topical therapy for plaque psoriasis from calcipotriene to tazarotene was completed in 246 patients undergoing combination therapy with a topical corticosteroid agent.<sup>33</sup> The study demonstrated significant improvement in efficacy and greater patient satisfaction correlated with the change from topical calcipotriene to tazarotene for up to 12 weeks. These results correlated with findings from a previous study evaluating a switch in therapy from topical calcipotriene to tazarotene with or without use of a topical corticosteroid.<sup>34</sup>

## Use of Tazarotene in Combination with Other Agents for Acne

A multicenter 12-week investigator-blinded trial of 440 patients (age > 12 years) with mild-to-moderate facial acne vulgaris evaluated the efficacy and tolerability of once daily tazarotene 0.1% gel monotherapy as compared to combination with twice daily use of benzoyl peroxide 4% gel, erythromycin 3%/benzoyl peroxide 5% gel or clindamycin phosphate 1% lotion.<sup>35</sup> A comparator group using topical clindamycin alone was also included. For efficacy against inflammatory lesions, tazarotene plus the erythromycin/benzoyl peroxide combination gel produced a 65% decrease in mean lesion counts compared to a range of responses approximating 40% with all other regimens, including tazarotene used alone. The greatest levels of global improvement by study endpoint was observed with tazarotene plus clindamycin lotion (77%) and tazarotene plus erythromycin/benzoyl peroxide gel (73%). Treatment success defined as 75 – 100% clearance of facial acne by week 12 was

greatest in the study group using the tazarotene-clindamycin regimen (67% versus 38 – 49%). All combination regimens were associated with transient development of local tolerability reactions such as dryness and erythema which was usually rated as mild. The range of patients reporting favorable overall impressions regarding their treatment in the combination therapy groups was 85 – 92% as compared to 73% with tazarotene monotherapy and 58% with clindamycin used alone. The percentage of patients reporting that they would continue treatment with the same regimen after study completion was highest in the combination therapy groups (86 – 93%). In the group treated with tazarotene alone, 76% indicated they would use the same treatment in the future and 65% found tazarotene monotherapy to be at least as effective or more effective than previously used acne medications.

A large open-label private practice experience trial was inclusive of 673 patients (age > 12 years) with mild-to-moderate facial acne vulgaris treated with tazarotene 0.1% gel once daily for 12 weeks in combination with at least one other topical acne medication, with or without oral antibiotic therapy.<sup>36</sup> Eighty percent used only one concomitant agent (clindamycin 27%, benzoyl peroxide 22%, erythromycin/benzoyl peroxide 14%). By week 12, mean percentage reduction in inflammatory lesion counts were decreased by 66% and 64% in patients using clindamycin/tazarotene and benzoyl peroxide/tazarotene, respectively, and 58% in patients using tazarotene as their sole topical agent. Tazarotene alone produced a 65% reduction in comedonal lesion mean percentage which was comparable to responses noted with tazarotene-containing combination regimens (56 – 67%). In 378 patients, the addition of topical tazarotene to an existing regimen was reported to provide an additional mean percentage reduction of 69% for comedonal lesions and 66% for inflammatory lesions, independent of whether or not patients were utilizing oral antibiotic therapy. Upon switching from another topical retinoid to tazarotene without any other changes in their regimen, in patients changed from tretinoin gel/cream or adapalene gel, an additional 56% and 65% reduction in comedonal lesions was observed, and an additional 51% and 56% reduction in inflammatory lesions was observed, respectively. A lesser degree in lesion count reductions were noted in patients changed from tretinoin 0.1% microgel (microsphere), with an additional 39% reduction in comedonal lesions and 27% reduction in inflammatory lesions correlated with the switch to tazarotene use.

<b>TRIAL</b>	<b>RESULTS</b>
<b>Leyden JJ, et al/Mild-Moderate Facial Acne Double-Blind Randomized 12-Week Trial/Age 12+ Years<sup>37</sup></b>	
Tazarotene 0.1% Gel Once Daily (n = 84)	>50 % Global Improvement: 67% Median Reduction Inflammatory Lesions: 56%* Median Reduction NonInflammatory Lesions: 60% Tolerability: Most reactions mild Irritation 13% / Erythema 11% / Dryness 7% Scaling 4% / Peeling 5% / Burning 11% Discontinuations due to reactions 2%
Tretinoin 0.1% Microsphere Gel Once Daily (n = 85)	>50 % Global Improvement: 49 % Median Reduction Inflammatory Lesions: 46 %* Median Reduction NonInflammatory Lesions: 38 Tolerability: Most reactions mild Irritation 4 % / Erythema 6 % / Dryness 6 % / Scaling 2 % / Peeling 1% / Burning 9 % Discontinuations due to reactions 2 %
<b>Webster GF, et al/Mild-Moderate Facial Acne/Double-Blind Randomized 12-Week Trial/Age 12+ Years<sup>38</sup></b>	
Tazarotene 0.1% Gel Once Daily (n = 72)	>50 % Global Improvement: 78 % Median Reduction Inflammatory Lesions: 70 % Median Reduction NonInflammatory Lesions: 71 % Tolerability: Most reactions mild Irritation 13 % / Erythema 3 % / Dryness 1% / Stinging 3 % / Peeling 6 % / Burning 8 % Discontinuations due to reactions 1%
Adapalene 0.1% Gel Once Daily (n = 73)	>50 % Global Improvement: 52 % Median Reduction Inflammatory Lesions: 55 % Median Reduction NonInflammatory Lesions: 48 % Tolerability: Most reactions mild Irritation 5 % / Erythema 0 % / Dryness 5 % / Stinging 0 % / Peeling 1% / Burning 3 % Discontinuations due to reactions 1%
<b>Webster GF, et al/Mild-Moderate Facial Acne/Double-Blind Randomized 12-Week Trial/Age 12+ Years<sup>39</sup></b>	
Tazarotene 0.1% Gel Once Daily (n = 72)	Mean Reduction Open Comedones: 65 % Mean Reduction NonInflammatory Lesions: 55 % Mean Reduction Inflammatory Lesions: 54 %* Tolerability: Most reactions mild / trace Irritation 6 % / Erythema 4 % / Dryness 6 % / Peeling 1% / Burning 7 % Discontinuations due to reactions 3 %
Tretinoin 0.025 % Gel Once Daily (n = 71)	Mean Reduction Open Comedones: 44 % Mean Reduction NonInflammatory Lesions: 42 % Mean Reduction Inflammatory Lesions: 44 %* Tolerability: Most reactions mild / trace Irritation 3 % / Dryness 3 % / Burning 3 % Discontinuations due to reactions 0 %
<b>Leyden JJ, et al/Mild-Moderate Facial Acne Double-Blind Randomized 15-Week Trial/Age 12+ Years<sup>40</sup></b>	
Tazarotene 0.1% Gel Once Every Other Day (n = 82)	>50 % Global Improvement: 74 %* Mean Reduction NonInflammatory Lesions: 55 %* Mean Reduction Inflammatory Lesions: 57 %* Tolerability: Most reactions mild / trace Discontinuations due to reactions < 1% Total Drug Usage: 29.9 grams
Adapalene 0.1% Gel Once Daily (n = 82)	>50 % Global Improvement: 73 %* Mean Reduction NonInflammatory Lesions: 58 %* Mean Reduction Inflammatory Lesions: 54 %* Tolerability: Most reactions mild / trace Discontinuations due to reactions < 1% Total Drug Usage: 87.2 grams
(*difference not statistically significant)	

## Cream Formulation of Tazarotene

Based on available data and clinical experience, the cream formulation of tazarotene appears to maintain efficacy and reduce the incidence of local tolerability reactions.

**Acne Vulgaris.** Two parallel-group, multicenter double-blind, vehicle-controlled studies inclusive of 847 patients with facial acne vulgaris, compared tazarotene 0.1% cream applied once daily for 12 weeks versus placebo vehicle.<sup>41</sup> Tazarotene 0.1% cream was significantly superior than vehicle in reducing total number of acne lesions, number of inflammatory lesions and number of non-inflammatory lesions. Tazarotene 0.1% cream was associated with a lower incidence of most signs and symptoms of local tolerability reactions as compared to incidence rates reported in studies evaluating tazarotene 0.1% gel, including stinging, burning, irritation and pruritus. One female patient discontinued tazarotene use at week 8 due to a positive pregnancy test and subsequently delivered a healthy child. Multiple sample evaluations of plasma tazarotenic acid levels were completed at weeks 4 and 8; the mean plasma level was 0.1 + 0.1 mg/ml, significantly lower than reported endogenous concentrations of tretinoin and its metabolites. Over the 8 week period of pharmacokinetic analysis, based on a total of eighty-nine samples, plasma tazarotenic acid levels did not increase over time with repeated daily tazarotene cream application.

**Photoaging.** A dose-response multicenter, investigator-blinded, vehicle-controlled, parallel-group study compared tazarotene 0.01%, 0.025%, 0.05% and 0.1% creams and tretinoin 0.05% emollient cream applied over 24 weeks for treatment of facial photodamage.<sup>42</sup> Treatment success rates based on global assessment at the end of treatment were highest for tazarotene 0.1% cream (67%, n = 58), tretinoin 0.05% emollient cream (55%, n = 58) and tazarotene 0.05% cream (52%, n = 58) as compared to vehicle (22%, n = 58). Tazarotene 0.1% cream demonstrated a trend toward quicker response than tretinoin. Histologic evaluations of tazarotene-treated skin demonstrated favorable changes in photodamaged skin including increased epidermal thickness and decreased melanin content. Consistent with other studies evaluating topical tazarotene in both gel and cream formulations, systemic exposure to tazarotenic acid was minimal with use of the tazarotene creams (0.02 – 0.1 ng/ml). Local irritation was seen most frequently in patients treated with higher

concentrations of topical tazarotene reported in most cases as mild to moderate in severity; in each treatment group, three subjects or less discontinued participation in the trial due to adverse effects.

In a 52-week multicenter vehicle-controlled trial inclusive of a 24-week double-blind phase (n = 511) and a 28-week open phase (n = 482), tazarotene 0.1% cream achieved significantly greater treatment success (>50% global improvement), and a minimum of 1-grade improvement in tactile roughness, fine wrinkling, coarse wrinkling, mottled and irregular dyschromia, lentiginos, elastosis and pore size.<sup>43</sup> Continued improvement was observed throughout both phases of the study with no plateau effect noted over 52 weeks of therapy. Plasma levels of tazarotenic acid were based on 60 actively treated patients from the first study phase and 48 patients from the second study phase. There was no evidence of drug accumulation or increased plasma concentrations with repeated daily tazarotene application over 52 weeks of therapy; mean plasma levels were consistently below 0.13 ng/ml and did not exceed 0.71 ng/ml.

## Use of Topical Tazarotene for Acne in Skin Types V or VI

A pilot study evaluated the use of tazarotene 0.05% gel once daily for 8 weeks in ten African-American and four Hispanic patients treated for mild-to-moderate facial acne vulgaris.<sup>44</sup> The first two weeks, a small quantity of tazarotene gel was applied along with an equal quantity of moisturizer. If no signs of intolerance were noted after two weeks, the tazarotene gel was then applied without moisturizer dilution. No adverse reactions or changes in pigmentary skin intensity were noted. At study endpoint, the mean inflammatory and noninflammatory lesion counts decreased by 52% and 77%, respectively.

## Reducing Local Tolerability Reactions Associated with Topical Retinoids

All currently available topical retinoids, including tretinoin, tazarotene, adapalene and retinol, are associated with a significant risk for the development of local tolerability reactions, referred to as “retinoid dermatitis”. Such reactions may be related to the vehicle properties, inherent properties of the specific retinoid, concomitant skin care practices or use of adjunctive skin care products that enhance the development of irritation. The role of vehicle in development of retinoid associated irritation has been defined by the “irritation history” of topical

tretinoin; the more recent availability of emollient, microsphere and polymer vehicles for tretinoin have at least partly reduced the potential for irritation. Of the available prescription-only topical retinoids, the adapalene 0.1% formulations have generally been associated with the lowest reported incidence of local tolerability reactions.

The availability of tazarotene in two strengths (0.05%, 0.1%), the addition of the newer cream formulation and the identification of appropriate application technique allows for adjustments in treatment and a lowered risk of application site reactions. Split-face evaluations of “sensitive skin” patients (history of rosacea or atopy) treated with tazarotene 0.1% gel, tretinoin 0.025% gel or adapalene 0.1% gel for up to 29 days demonstrated comparable increases in facial dryness and erythema.<sup>45</sup> Use of moisturizers were excluded. The authors concluded that the need to adjust or modify topical retinoid therapy is more dependent on individual patient tendency than on the inherent differences in the irritation potential of specific topical retinoids. A blinded analysis specifically evaluating once versus twice daily application of tazarotene 0.1% gel demonstrated superior tolerability with the use of an alternate day (every other day) regimen at the initiation of therapy for the first two weeks.<sup>45</sup>

In later studies evaluating once daily use of topical tazarotene 0.1% or 0.05% gel, lower reported rates of local tolerability reactions were correlated with the use of specified skin care instructions.<sup>39</sup> When using topical tazarotene, irritation may be avoided by instructing patients to:

- Cleanse with a gentle skin cleanser
- Apply no more than a pea-sized amount of medication
- Use a noncomedogenic, nonfragranced moisturizer
- Initiate therapy every other day for the first two weeks then progress to daily application if no significant local application site reactions are noted

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# Segmental Variant of an Unusual Tumor: Case Presentation and Review of the Literature

By Dan Ladd, D.O., Rick Lin, DO, MPH, Dermatology Residents, KCOM/Texas Division, Program Director: Bill V. Way, D.O.

## Abstract

*Tubular apocrine adenoma (TAA) is a rare cystic tumor that is easily treated with excision. Because atypical variants of this tumor share many features with apocrine adenocarcinoma, precise guidelines for appropriate management may be elusive. This paper presents a case of TAA and review of the literature to better elucidate this rare entity.*

## Case Presentation:

A 43 yo African-American female presented to our clinic with a complaint of “knots” on the buttocks, asymptomatic, which seemed to be spreading for 25 years. Most recently the lesions had started to ulcerate. Clinical examination revealed smooth dome shaped violaceous to black nodules clustered in a linear array in various sizes. The largest nodules were approximately 20 x 15mm in diameter. Mild ulceration was seen in some of the lesions. The digital photograph below depicts these lesions in the gluteal cleft.

## Background:

TAA is an uncommon cystic lesion which is benign. While the lesions are typically solitary, there have been reports of multiple lesions. Presentation varies, but usually TAA presents as a solitary papule, up to 1.5 cm, dome shaped, translucent or bluish/black. It may be clinically misdiagnosed as cystic basal cell carcinoma, pigmented basal cell carcinoma, and even melanoma resulting at times to inappropriately aggressive surgical intervention. This highlights the importance of obtaining biopsy results before planning surgical intervention.

Histologically TAA is characterized by numerous irregularly shaped tubular structures, some with dilated lumens with papillary projections. At times these structures project so excessively into the lumen that they form bridging type intraluminal hyperplasia. TAA may have verrucous architecture resembling syringocystadenoma papilliferum, but it lacks the plasma cell rich stromal inflammatory infiltrate seen in syringocystadenoma papilliferum. In fact, the stroma surrounding TAA is markedly fibrous and has very few inflammatory cells. The cystic structures in TAA typically have a double layer of cells. The luminal cells tend to be cuboidal whereas the peripheral cells tend to be flat. Decapitation secretion of the luminal cells is characteristic of apocrine differentiation. The cystic tubular structures are not continuous with the

epidermis. The treatment is simple excision. H&E histology from this case is presented in the digital photomicrographs below.

## Literature Review:

Jadassohn in 1914 defined “Adenoma” as having atypical glandular structures in contrast to simple enlargement or more numerous typical glands found in the nevus sebaceous of Jadassohn.

Tappener in 1947 and Civatte et al in 1964 all noted that TAA is microscopically distinct from apocrine hidrocystoma, nevus sebaceous of Jadassohn, hidradenoma papilliferum, syringocystadenoma papilliferum, apocrine mixed tumor or papillary apocrine hidrocystoma. They noted that Hidradenoma papilliferum has a more arborizing and trabeculated pattern than TAA. Syringocystadenoma papilliferum has an inflammatory infiltrate rather than the fibrous stroma seen in TAA.

In the paper by Landry et al. entitled “An Unusual Tubular Apocrine Adenoma” a 66 yo woman with a 7 x 4 cm pedunculated, exuberant tumor with cerebriform surface on the scalp was presented. This case was unusual because the TAA arose in a pre-existing nevus sebaceous of Jadassohn she had since birth. The tumor was excised with no recurrence after 1 year. A histochemical analysis of the specimen revealed evidence for apocrine differentiation including decapitation secretion and positive staining for indoxyl esterase and acid phosphatase. The possibility of eccrine differentiation was cast into doubt as the specimen failed to stain with phosphorylase.

Umbert et al. in their paper entitled “Tubular Apocrine Adenoma” repeated the findings from Landry’s case and added a second newer case. This time the patient was a 23 year old white male who presented with a 2 x 1 cm nodule vertex scalp that had been present for several years. This was an interesting case because the original histologic diagnosis was metastatic adenocarcinoma. This patient had no evidence of cancer in



Figure 1

the GI tract. The lesion was treated with wide excision, and no recurrence was seen at 1 year. Histologically this tumor revealed decapitation secretion and stained positively for markers of apocrine differentiation such as indoxyl esterase, acid phosphatase and leucine aminopeptidase. Apocrine tubules were well differentiated in some areas and poorly differentiated in others. The article detailed a number of parameters that might help the pathologist to favor a diagnosis of TAA over metastatic adenocarcinoma as follows: organoid differentiation, high degree of cellular differentiation, connection to epidermis, absence of mitotic figures and absence of cellular anaplasia.

“Apocrine Gland Adenoma and Adenocarcinoma of the Axilla” by Warkel et al. reviewed 12 patients with axillary apocrine tumors. Two of those patients were diagnosed with TAA and were alive at 3 and 4 years after excision. Eight were diagnosed with adenocarcinoma, and of those 2 died of unrelated causes (heart attack and stroke), 3 died of adenocarcinoma, 1 was alive with skeletal metastasis. The remaining 4 diagnosed with adenocarcinoma were alive and well at 3 year follow ups and one was found to be alive at a 15 year follow up. In comparing the histologic features of TAA to those of apocrine adenocarcinoma, the following features of apocrine adenocarcinoma were highlighted: poor cellular differentiation, linearly infiltrating pleomorphic tumor

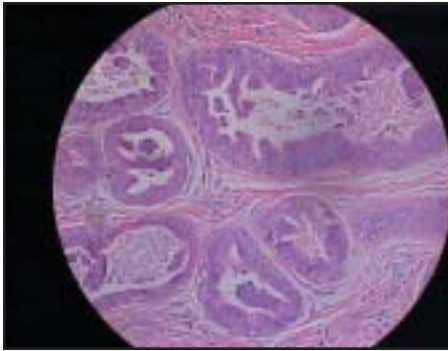


Figure 2

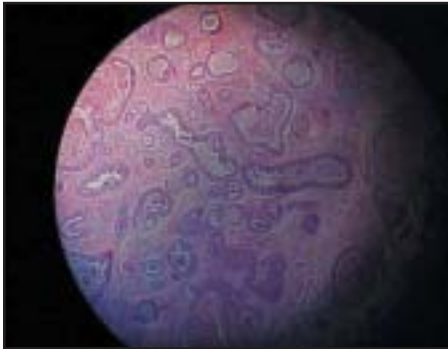


Figure 3



Figure 4



Figure 5

cells with stromal desmoplasia and hyperplasia with frank neoplasia.

Okun et al reported in their article entitled "Apocrine Adenoma versus Apocrine Carcinoma" 2 cases of TAA. One was clearly benign but the other had moderate nuclear pleomorphism, which led 3 of 8

pathologists to diagnose apocrine adenocarcinoma rather than TAA. Graham, Johnson & Helwig believe recurrent TAA of the axilla is frequently misdiagnosed as adenocarcinoma.

In the article entitled "Perianal Apocrine Gland Adenoma" Weigand et al described a 59 year old with a perianal pedunculate tumor, originally misdiagnosed as condyloma acuminata, which had failed treatment with topical podophyllum resin. Histology was consistent with TAA and treatment was simple excision with no recurrence.

In the article by Burket et al entitled "Tubular apocrine adenoma with perineural invasion" a tumor on the scalp with features of TAA and syringoid eccrine carcinoma was described. Perineural invasion was present. Perineural invasion is common in syringoid eccrine carcinoma but had never been reported in tubular apocrine adenoma at the time this article was printed. Burket et al. felt the infiltrative and invasive features seen in their case broadened the category of TAA so that it would no longer be considered completely benign. The recommendation was to manage TAA as you would other locally aggressive malignancies.

Zulaica et al in their paper entitled "Tubular Apocrine Adenoma" described a 33 yo woman with foul smelling tumor on posterior scalp x 6 months. Histopathology revealed features of syringocystadenoma papilliferum, including papillomatous surface changes and an inflammatory infiltrate rather than a purely fibrous stroma. Again treatment was simple excision.

### Discussion

A review of the literature reveals that tubular apocrine adenoma is a rare tumor that has histological features that may overlap with a number of entities including apocrine adenocarcinoma, hidradenoma papilliferum, apocrine hidrocystoma, mixed apocrine tumor, syringoid eccrine carcinoma and syringocystadenoma papilliferum. Given this confusing multitude of diagnostic dilemmas, the bottom line in patient care becomes the age old decision of "benign v. malignant".

Several of the articles mentioned above site cytologic features as the best way to rule out malignancy in these lesions including pleomorphism, degree of cellular differentiation, stromal desmoplasia, degree of infiltration of tumor, hyperplasia and of course frank neoplasia. Special stains may be used to differentiate eccrine from apocrine origin, but are of little use in settling the question of malignancy.

Our patient remains tumor free 3 years after excision and histologically her tumor lacked features that would suggest malignancy. Our case was unusual because the presentation was that of a linear or segmental grouping of nodular lesions rather than a single nodule or tumor. To our knowledge this is the first reported case of segmental or linear variant of tubular apocrine adenoma. Review of the literature reveals that pathologists and clinicians should be vigilant for cytologic features of malignancy in these unusual tumors and that follow up should be performed at regular intervals.

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# Neonatal Lupus Erythematosus: Case Report and Review

Raymond A. Schwab, D.O., Lieutenant Colonel, US Air Force, Medical Corps, Wright-Patterson Air Force Base, Ohio

## Abstract

Neonatal Lupus Erythematosus is a multisystem disorder with cutaneous, cardiac, hematologic and hepatobiliary manifestations. Transplacental passage of maternal autoantibodies to the fetus from women with either Systemic Lupus Erythematosus, Sjogrens Syndrome or an undifferentiated autoimmune disease is the accepted cause. A case report of Neonatal Lupus Erythematosus and literature review is presented.

## Report of Case

A 7-week-old male infant was referred for dermatologic evaluation of a rash present since three weeks of age. The rash was widespread and located on the head, neck, chest, abdomen, arms, and in the diaper region. Prior treatment with topical moisturizers and hydrocortisone cream were not helpful. Previous skin scrapings for fungal culture were negative. The infant was born at term and in a normal state of health. He was afebrile and had no known associated illnesses. Prior to delivery, the infant's mother was being followed for an undetermined autoimmune disorder associated with intermittent facial rash, and serologies positive for antibodies to SSA/Ro and SSB/La.

Examination of the infant's skin revealed scattered annular erythematous macules and patches ranging from 2mm to 20mm in size. Areas of annular erythema were present on the scalp, forehead, eyelids, neck, trunk, arms, and in the suprapubic area (Figures 1 and 2). There was no evidence of scale or other cutaneous changes. A mild erythema was noted on the cheeks bilaterally. The palms and soles were clear. Repeat skin scrapings for potassium hydroxide evaluation were negative for fungal elements.

Laboratory evaluation of the infant was significant for a positive antinuclear antibody (ANA) at a titer of 1:2,560 in a speckled pattern. Additional antibody studies were positive for both SSA/Ro and SSB/La antibodies. All other laboratory tests to include a complete blood count with platelets, liver and renal function tests were within normal parameters. A rapid plasma reagin test was non-reactive. Cardiac evaluation by an electrocardiogram was significant for a normal sinus cardiac rhythm without evidence of heart block. A diagnosis of Neonatal Lupus Erythematosus was made based on clinical and laboratory findings. Treatment was started with topical desonide cream twice daily. Photoprotective mea-

asures were also instituted. Complete resolution of all areas of annular erythema occurred within five weeks. Repeat laboratory testing for ANA, SSA/Ro and SSB/La antibodies turned negative by six months of age. The child remains healthy to date and free from cutaneous, cardiac, or autoimmune disease.

## Discussion

Neonatal Lupus Erythematosus (NLE) is an uncommon disorder that may require dermatologic evaluation for diagnosis. The incidence of NLE is 1 in 12,500 live births.<sup>(1,2)</sup> The accepted cause of NLE is from transplacental passage of maternal autoantibodies to the fetus from women with either Systemic Lupus Erythematosus, Sjogrens Syndrome or an undifferentiated autoimmune disease.<sup>(1-13)</sup> A reported 50% of women are asymptomatic at the time of delivery. However, the vast majority of these women develop some form of connective tissue disease over time.<sup>(1-3,7,9-15)</sup> Specific autoantibodies involved in NLE include SSA/Ro and/or SSB/La antibodies.<sup>(1-18)</sup> SSA/Ro is considered the antibody marker in NLE and found in over 90% of cases.<sup>(1,7,9,11,14,16-18)</sup> Less commonly reported autoantibodies include ANA, dsDNA, U1RNP and Scl-70.<sup>(1-3,6,8,11,16,19)</sup> These maternally acquired autoantibodies are transient in the infant and clear from the infant's circulation by six months of age.<sup>(1-3,7,8,12,14,18)</sup> The major clinical features of NLE involve the skin and heart.

Cutaneous features of NLE occur in 50% of patients and consist of a characteristic annular erythema.<sup>(1-3,6,7,9-11,13,14,16)</sup> Annular erythematous macules and patches appear at birth or within the first few weeks of life. The annular erythema has a predilection for the head and neck but may involve other skin areas as seen in this case. The pathogenesis of skin disease in NLE involves the binding of SSA/Ro, SSB/La and other autoantibodies to the basal keratinocytes.<sup>(3)</sup> Skin disease is exacerbated by ultraviolet light; therefore, photoprotection is helpful in the treatment of the cutaneous manifesta-



Figure 1



Figure 2

tions of NLE.<sup>(2,3,5,7,10,11,14,16)</sup> Other treatment options for the cutaneous features of NLE include the use of nonfluorinated topical corticosteroids.<sup>(3,5,14,16)</sup> Regardless of treatment, the skin lesions of NLE are self-limited. Resolution of skin lesions correlates with the clearance of maternal autoantibodies from the infant's circulation at six months of age.<sup>(1-3,5,7,10-14,16,18)</sup> Scarring is an unusual sequelae of cutaneous disease. However, hypopigmentation, epidermal atrophy and persistent telangiectases may follow the rash of NLE.<sup>(1,2,7,11,14,16)</sup> Skin biopsy of the annular erythema in NLE displays epidermal atrophy with hydropic degeneration of the basal layer. A superficial mononuclear cell infiltrate predominates. Biopsy findings mimic those of subacute cutaneous lupus erythematosus.<sup>(2,3,6,10,11,14,16)</sup>

Cardiac involvement in NLE occurs in 50% of patients and represents the most serious manifestation of the disease.<sup>(1-3,7,19)</sup> Complete congenital heart block (CCHB) is the major cardiac finding. CCHB is an irreversible, third degree, atrioventricular (AV) block. Significant morbidity and mortality is associated with CCHB due to

the development of congestive heart failure. (1-4,6-16,19) Placement of a permanent pacemaker is required in two-thirds of infants with CCHB in NLE. Regardless of therapy, a reported 15-30% mortality rate occurs in infants with CCHB in NLE. (1,3,7,10,13,14) CCHB can be detected as early as 16-18 weeks gestation by fetal echocardiogram. Fetal echocardiogram will reveal evidence of either a bradycardia or an arrhythmia. (1-4,6,11-14) The pathogenesis of CCHB in NLE is due to fibrosis and calcification in the area of the AV node. The fetal cardiac conduction system appears vulnerable to SSA/Ro and SSB/La autoantibodies during cardiac embryogenesis. (6,13,14,18) After birth, CCHB can be detected by an electrocardiogram. The maternal risk for delivering an infant with CCHB in primigravida women with SLE is 1-2%. However, this risk increases to 25% with subsequent pregnancies. (1,4,10,11) Therefore, appropriate counseling of these women and serial fetal echocardiograms are warranted in all pregnancies. Case reports have described the use of systemic corticosteroids such as dexamethasone and prednisolone in pregnant women with fetal echocardiographic evidence of complete AV block. The systemic corticosteroids completely or partially diminished the AV block in the infants at the time of birth. (6,13) Unfortunately, these results have not been proven universally effective. Infants presenting with both the cutaneous and cardiac features of NLE are seen in only 9% of cases. (3)

Hematologic abnormalities are found in 10-20% of patients with NLE. (1-3,5,7,10,14,18) These include anemia, thrombocytopenia, and leukopenia. Appropriate supportive measures are helpful for these transient features of NLE. Hepatobiliary involvement may develop in 20%- 40% of patients with NLE. Manifestations may range from mild transaminasemia and hyperbilirubinemia to rarely reported liver failure. (1-3,6,7,10,14,18,20) Children with a history of NLE do not have an increased risk of developing SLE. However, the development of some form of autoimmune disease in early childhood may occur. Examples include juvenile rheumatoid arthritis, Hashimoto's thyroiditis, psoriasis, diabetes mellitus and hypothyroidism. (19) This risk necessitates continued medical surveillance of these patients throughout childhood.

NLE is an uncommon disorder with a characteristic presentation. The first clue to NLE maybe the finding of a bradycardia or an arrhythmia on fetal echocardiogram. Infants present with either the skin rash of annular erythema, complete congenital heart block or both. Associated features of NLE may include hematologic and hepatobiliary abnormalities. The der-

matologist plays a vital role in the early recognition and diagnosis of NLE. Early diagnosis may improve the morbidity and mortality of NLE.

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## Figure Legends

Figure 1 and Figure 2: annular erythematous macules and patches of Neonatal Lupus Erythematosus.

### Correspondence:

Raymond A. Schwab, D.O.  
Lt. Col, USAF, MC  
Dermatology Element  
4881 Sugar Maple Drive  
Wright-Patterson AFB, Ohio 45433  
Phone: 937-257-1574  
Fax: 937-257-4119  
E-mail: [Raymond.Schwab@WPAFB.AF.MIL](mailto:Raymond.Schwab@WPAFB.AF.MIL)  
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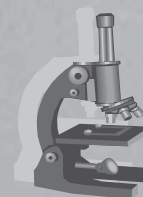
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