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COPY EDITOR
JULIA LAYTON BA, MFA
LAKewood, CO
The JAOCD is now well into its ninth year as the journal representing our college and our residency programs. To the best of my knowledge, we are one of only two specialty colleges within the AOA that has its own journal, and we should be very proud and supportive of it.

You will notice that we have changed the cover of the JAOCD. Now, each month, the cover will depict either a clinical or dermatopathology photograph from a case, with reference to the page on which it is contained in a specific manuscript. The graphics have also been changed, and we hope it becomes the new face of the JAOCD.

We now have 53 Associate Editors on board. Each Associate Editor has agreed to review three to four manuscripts each year for medical content. Julia Layton, our copy editor, has taken on the day-to-day running of the journal, and she has been doing an outstanding job.

Dr. Jon Keeling remains the Co-Editor of the journal. Dr. Jay Gottlieb is the Founding Editor and remains the Editor-in-Chief, responsible for the overall direction of the journal and maintaining sponsor relationships.

Our journal could not exist without the continued support of our Sponsors. Without the backing of Global Pathology, Medicis, Galderma, Ranbaxy and Intendis, there would be no JAOCD. Our sincere thanks go out to each of our dedicated and loyal AOCD sponsors.

Each of the Associate Editors will be receiving a beautiful certificate, definitely suitable for and deserving of framing. Each JAOCD Sponsor will be receiving a similar certificate. These will be mailed out this month.

Julia Layton has been looking into having the JAOCD indexed with PubMed. We have achieved the status of being a fully peer-reviewed medical journal that is published quarterly, and we hope to meet the further requirements within the next six months.

Most important, we need to have quality manuscripts submitted by our membership and resident membership. We must have the program directors review, correct and approve each resident’s manuscript before it is submitted for consideration for publication in order to ensure that it is, in fact, suitable for publication. The JAOCD does not have the staff to take on this responsibility, and the EEC has made this the responsibility of each program director.

All in all, the JAOCD is doing quite well, growing and thriving, and will continue to do so with the increased support of our membership.

Sincerely,

Jay Gottlieb, DO, FAOCD
Senior Chief

Jon Keeling, DO, FAOCD
Co-Editor
Hi, Everyone,

It has been a very busy summer in the AOCD office. On June 15th, the AOCD welcomed two new employees to the office in Kirksville.

**John Grogan** is our new Resident Coordinator/Member Support. His email is jgrogan@aocd.org.

John earned his Bachelor of Arts degree in English with a dual emphasis in technical communication and literature from Missouri Western State University. He began his career in 2006 as a content developer with Cerner Corporation in Kansas City, Missouri. John and his wife, Angel, relocated to Kirksville, where he accepted a position with KTVO, the local ABC affiliate, as the director of programming and sales coordinator in 2008. We are so pleased he has decided to join us in 2011.

**Carmen Stanton** is our new Coordinator of Grants and Corporate Support. Her email is cstanton@aocd.org.

Carmen earned a marketing degree from the University of Nevada, Las Vegas, where she spent more than a decade working in television production. Since her return to Missouri in 1998, she has worked primarily in non-profit management and real estate. Carmen developed the state- and nationally-recognized Northeast Missouri Medical Reserve Corps, one of three grant-funded pilot programs in Missouri, and spent time at the helm of the North Central Chapter of the American Red Cross. Before coming on board the AOCD, she was a real estate agent and home stager. Carmen and her husband, Jim, a local concrete contractor, are avid NASCAR fans.

John and Carmen will attend the annual meeting, so please take a moment to introduce yourselves to them in Orlando. I am both blessed and honored to have John and Carmen join me here in the AOCD National Office. Their fresh perspectives and strong organizational skills have been a tremendous help.

In early June, Dr. David Grice and I met with the Hilton Staff in Branson, Missouri, and toured the facilities. I have to admit, it is not the Branson I remember from my last trip there. The date has been changed for the 2012 Midyear Meeting in Branson. The meeting is now scheduled for April 19-22. Lectures will be held from 1 p.m. until 6 p.m. on Thursday; 7 a.m. to 6 p.m. on Friday; 8 a.m. to 12:30 p.m. on Saturday; and 7:30 a.m. to 11:15 a.m. on Sunday. We hope to have a tentative schedule of topics and speakers available for you in Orlando. Please check our registration table for up-to-date information on our Midyear 2012 meeting. We look forward to you joining us in Branson.

July was busy with the AOA’s Annual Board of Trustee Meeting and House of Delegates. The AOCD Item Writers also met in July in St. Louis, where the group received instruction from psychometrician Dr. Terry Tenbrink.

In addition to the AOA House of Delegates, I attended the Postdoctoral Training Review Committee (PTRC) and the Council
on Postdoctoral Training (COPT) meetings in July in Chicago.

As I mentioned in the previous edition of the JACOD, the “ART” theme of Accountability, Reliability, and Transparency was a goal that I planned to work towards for the AOCD. Dr. Kramer and I have worked this past year on “Getting the AOCD ducks in a row,” and we’ve made significant progress.

Plan to attend the AOCD General Business meeting on Monday, October 31 at 3pm in Orlando at the Peabody. This will be your opportunity to vote for AOCD Officers. The Board of Trustees is elected to represent you. Please attend this meeting, vote, and share your concerns and comments with the members of the Board.

Residents are encouraged to submit their yearly papers to the JAOCD. Please remember to have your Program Director review this very important requirement before submitting it. We have so far reviewed 100 resident annual reports out of the 108 due to us for this training year, and 41 residents have submitted their yearly REQUIRED paper to the JAOCD.

As fall approaches, I look forward to catching up with everyone in Orlando and to the addition of two new grandchildren.

Your continued support of the AOCD and the JAOCD is vital for growth. Thank you to all of our valued members. This has been a good year for the AOCD!

Sincerely,

Marsha A. Wise

Executive Director, AOCD
Blisters in the Newborn: Differential Diagnosis and Review

Risa Behar Ross, DO,* Richard A. Miller, DO, FAOCD**
* 3rd-year Dermatology Resident, Nova Southeastern University, Largo Medical Center, Largo, Florida
** Dermatology Residency Program Director, Nova Southeastern University, Largo Medical Center, Largo, Florida

ABSTRACT

Blisters in the newborn can be quite concerning for new parents and caregivers. Pediatricians are usually the first to examine the neonate, and it is important for them to correctly identify transient blistering conditions to reassure anxious parents. It is essential for pediatricians to work with their dermatologic colleagues in order to recognize life-threatening blistering conditions and obtain necessary consultations in a timely fashion. Blisters in the newborn can be classified into transient, infectious, due to inherited diseases, as well as other subcategories. The purpose of this review is to discuss blistering conditions in each of the categories including key diagnostic features, treatment options, and prognosis.

Introduction

Transient neonatal blistering conditions are commonly encountered by the pediatrician, and dermatologic consult is often not necessary. Other blistering conditions, although some may be benign and transient, do require dermatologic evaluation. Some examples of transient neonatal blistering conditions are sucking blister, erythema toxicum neonatorum, miliaria, transient neonatal pustular melanosis, acropustulosis of infancy, and neonatal cephalic pustulosis. A few examples of infectious etiologies of blistering conditions may include herpes simplex virus, staphylococcal and streptococcal infections, varicella, and scabies. Some inherited causes of blisters in the newborn include epidermolysis bullosa and incontinentia pigmenti. Other conditions to consider when evaluating a newborn with blisters include neonatal Behcet’s disease, pustular psoriasis, Langerhans cell histiocytosis, mastocytosis and maternal autoimmune disease.

Transient Eruptions

Sucking blisters

Sucking blisters present most commonly as 0.5-2.0 cm, flaccid bullae or erosions on the upper extremities, specifically on the radial forearm, wrist, or hand. They are thought to be a result of vigorous sucking by the infant in utero.1 At times, the neonate can be observed sucking the affected area.2 Due to the distinct clinical presentation, this entity is very rarely reported in the literature, and the true incidence is unknown. The most recent review was in 1963 by Murphy and Langley, who reported the frequency of sucking blisters to be 1 in 250 births.3 Biopsy is not recommended, and treatment is not necessary. Sucking blisters resolve rapidly and spontaneously without scarring or other lasting effects.

Erythema toxicum neonatorum

Erythema toxicum neonatorum (ETN) is another commonly encountered blistering disease of the newborn. Again, this entity is rarely encountered by the dermatologist as it is so commonly seen by the pediatrician. Often times, the eruption has resolved by the time dermatologic consultation is available. ETN classically appears as blotchy, erythematous macules, papules, and pustules, presenting diffusely on the body, with a tendency to spare the palms and soles. ETN presents most commonly during the first 36-48 hours of life. Individual lesions can last from a few hours to several days.4 Biopsy is not indicated for classic-appearing ETN; however, if a biopsy were performed, histology would show eosinophils within the pilosebaceous apparatus. Treatment is not necessary for ETN, as it resolves spontaneously without sequelae.

Miliaria

Miliaria is caused by occlusion of the eccrine apparatus. There are variants of miliaria, which occur in the level of occlusion (Figure 1). Superficial occlusion of the eccrine duct is known as miliaria crystallina. This is commonly encountered in the neonatal period in hot, tropical climates. It consists of 1-2 mm vesicles most commonly on the head, neck, and trunk.5 Haas et al. did report a case of congenital miliaria crystallina, which is very rare.6 These vesicles tend to desquamate and resolve within hours to days of onset without any lasting effects. Miliaria rubra is a deeper obstruction of the eccrine unit. It is also known as “heat rash.” Clinically, this eruption appears as erythematous papules and pustules mainly on covered areas. With proper cooling measures, including lightweight clothing and cool baths, miliaria rubra resolves. Miliaria profunda is the deepest obstruction of the eccrine apparatus and tends to be limited to the trunk and extremities. There may be an associated local hypohidrosis or anhidrosis.7 This form is rarely encountered in the newborn. Miliaria crystallina and miliaria rubra are another example of benign, transient blistering eruptions in the newborn.

Transient Neonatal Pustular Melanosis

Transient neonatal pustular melanosis (TNPM) is a rare, asymptomatic blistering condition in neonates. It is more commonly seen in darkly pigmented individuals. TNPM occurs in the distinct phases, beginning with initial vesiculopustules, followed by development of fine scale with a collarette, and finally healing of the lesion as a hyperpigmented macule which eventually fades.8 A smear performed on the vesicles would show a predominantly neutrophilic infiltrate. TNPM usually begins at a few months of age, and patients continue to have eruptions over the following 2-3 years that follow a similar clinical pattern to that described above. Parents can be reassured that time between eruptions will lengthen, with eventual resolution of all symptoms.

Acropustulosis of Infancy

Acropustulosis of infancy is another blistering condition seen in newborns. Acropustulosis presents as scattered pustules on the palms and soles, as the name suggests. However, patients can also get lesions on the wrists, hands, ankles, and potentially even on the face and scalp. Acropustulosis is often pruritic, and the clinician must rule out an underlying scabetic infection. The etiology is unclear; however, some have reported scabies to be a triggering factor for the onset of acropustulosis. Episodes tend to recur every few weeks to months, with progressively less pruritus, fewer lesions, and longer remission periods. The cyclic outbreaks tend to resolve over 2-3 years. This condition can be quite frustrating for the parents and the patients. If the pruritus is severe, patients can be treated with antihistamines and topical steroids to provide symptomatic relief. Parents can be reassured that the episodes will eventually subside, and the patient will not have any lasting effects.

Neonatal Cephalic Pustulosis

Neonatal cephalic pustulosis, previously referred to as neonatal acne, is a commonly encountered eruption of newborns. There are various theories regarding etiology, including maternal hormones and the role of Malassazia species. A study done by Niamba et al. concluded there was a strong correlation between an inflammatory reaction caused by Malassazia species and neonatal cephalic pustulosis.9 Neonatal cephalic pustulosis can be cosmetically unpleasant, but parents can be reassured that the eruption will resolve without any scarring or other side effects.
Infectious Eruptions

Neonatal herpes simplex virus

Neonatal herpes simplex virus (HSV) is a concerning blistering disease in the newborn. Neonatal herpes infection could potentially be a devastating and lethal disease. Most infections are acquired via exposure during delivery. Neonatal herpes infection can be classified by extent of involvement. Those infections that are confined to the skin, eyes, and mucosa account for about 45% of the total number of infections. Skin manifestations include blistering and erosions in a localized or generalized distribution. It is important to recognize HSV and initiate prompt systemic therapy to prevent further dissemination and systemic involvement. Neonates with solely cutaneous manifestations who receive early intervention with antiviral therapy tend to do quite well, with minimal lasting effects. Neonates with CNS involvement have more significant sequelae including developmental delay, seizure disorders, blindness and cognitive disorders. Disseminated HSV can lead to multiorgan failure and is associated with increased mortality, even in the setting of antiviral therapy. HSV should be considered in any neonate with blisters.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) presents as an exfoliative dermatitis after a staphylococcal infection. SSSS is often seen in young children, who recover with appropriate antibiotic treatment. SSSS is more worrisome in neonates, where it can occur in outbreaks in newborn nurseries. SSSS presents as flaccid bullae, commonly in flexures, that develop within 48 hours of infection. Bullae are produced as an exfoliative toxin (ET-A, ET-B) is produced by the bacteria targeting Desmoglein-1, an important component of cell-to-cell adhesion in the upper layers of the epidermis. Appropriate antibiotic therapy results in resolution of desquamation within 24 hours and healing without scarring.

Neonatal Varicella

Another blistering disease of the newborn that is critical to recognize is neonatal varicella infection. Varicella, caused by varicella-zoster virus (HHV-3), is classically described as one of the TORCH infections of neonates that have serious consequences and associated mortality. Neonatal varicella infection presents as scattered erythematous vesicles on an erythematous base that appear within the first two weeks of life. Neonatal varicella may be caused by maternal varicella infection during the last three weeks of pregnancy or exposure to the virus after birth. Infections due to intrauterine exposure present earlier in life, whereas infection due to postnatal exposure to the virus tends to occur later in life. Congenital varicella syndrome (CVS) may also occur if the mother is exposed to the virus early in the pregnancy. Intrauterine varicella infection in the first 28 weeks of gestation may cause CVS resulting in limb deformities, brain abnormalities, and mental retardation. Eruption of maternal rash five days prior to two days after delivery tends to cause more serious infections. Prompt identification of varicella virus via serology and viral culture is vital, as late congenital and neonatal varicella can have up to a 30% mortality rate. These newborns are considered infectious and must be isolated and treated without delay. Treatment of these neonates includes varicella-zoster immunoglobulin and intravenous acyclovir.

Scabies

Scabies infestation, caused by Sarcoptes scabiei, is a relatively common disease amongst individuals residing in crowded living conditions. It typically presents as pruritic papules and vesicles in particular hands, wrists, umbilicus, and around the waist band. In newborns, it may also present on the genitilia. Scabies infestation can present as a vesicular disease in newborns, usually three to four weeks or older, and must be differentiated from other causes of blisters in the newborn. Positive identification of organisms as well as family history of similar eruptions is helpful in the diagnosis. Treatment for newborns greater than two months of age with scabies infestation is permethrin 5% cream applied topically, which is usually quite effective. Scabies is another entity that must be considered when encountering a newborn with blisters.

Inherited Diseases

Epidermolysis Bullosa

Epidermolysis bullosa (EB) is an example of a disease that could cause blisters in the newborn. EB can be further subdivided into epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), and dystrophic epidermolysis bullosa (DEB) depending on the genetic defect and resultant cleavage plane in the epidermal basement membrane (Table 1). Within each of these classifications, further subtypes were recently described by Fine et al., which depend on clinical features. EBS has various sub-classifications including Weber-Cockayne and Koebner variants, which account for most of the cases. Dowling-Meara variant and EB with muscular dystrophy are also recognized variants, along with other rare subtypes. Weber-Cockayne variant presents in early life. Most non-scarring, tense, painful bullae concentrated on the palms and soles. Onset of clinical findings can vary from birth to teenage years and tends to improve with age. Koebner variant also presents as non-scarring bullae on the palms and soles; however, these patients also have blisters on other sites, mainly at sites of friction. Oral blisters have been described as well in these patients. As with the Weber-Cockayne variant, the condition improves with age. Warmer weather tends to be most troublesome for these patients. Dowling-Meara variant is the most severe of the EBS subtypes. Clinically, these patients present with bullae in a herpetiform distribution on the trunk and limbs that may occur as early as birth to the first few weeks of life. Most patients due to a defect in genes encoding keratins 5 and 14, inherited in an autosomal-dominant manner. One exception is EB with muscular dystrophy, which is inherited in an autosomal-recessive manner and in which the antigenic target is plectin. Gene therapy will likely be a treatment for all types of EB in the future, as many advances have been made in this area. Currently, however, treatment is aimed at prevention of blister formation and local wound care.

Junctional epidermolysis bullosa (JEB) is the rarest type of epidermolysis bullosa. There are subtypes of JEB, all inherited in an autosomal-recessive manner, of which we will discuss JEB non-Herlitz and JEB Herlitz. JEB non-Herlitz with the Herlitz subtype present with extensive cutaneous fragility at birth. These neonates have diffuse blisters and erosions encompassing most of the body. These blisters heal with atrophic scarring, webbing, contractures, and milia. Extracutaneous involvement is extensive, as blisters can occur on any mucosal surfaces, including the gastrointestinal tract, urinary tract, and upper respiratory tract, all with similar sequelae as seen in the skin. Prognosis for these neonates is poor, and death typically occurs within the first few years of life. JEB non-Herlitz is a less severe form of JEB. These patients present with blisters in a generalized, localized, or inverse distribution. Blisters typically heal with atrophic scars, pigmentary alteration, alopecia, nail dystrophy, and dental abnormalities. Immunofluorescence and mapping studies may need to be performed to correctly classify these patients, as clinical presentation can vary and JEB non-Herlitz may present in a similar fashion to other types of EB. Overall prognosis tends to be favorable with a normal life span. The most crucial time period for individuals with JEB non-Herlitz is infancy, as these patients are at increased risk for secondary infections, fluid disturbances, and systemic absorption of topical medications. Correct diagnosis of these neonates is essential to ensure delicate handling and avoidance of any adhesives or other exogenous trauma. Treatment is aimed at prevention of blister formation and aggressive wound care. Gene therapy research has thus far been promising and will likely play a key role in treatment in the future.

Dystrophic epidermolysis bullosa (DEB) can be divided into dominantly inherited DEB (DDEB) and a recessive form of DEB (RDEB). DDEB and RDEB have a similar molecular basis, with abnormalities in collagen 7. Both have further sub-classifications. DDEB has...
milder clinical features, including blistering most commonly on the extremities that heals with scarring and milia. Blisters begin at birth or in the early weeks of life and tend to improve with age. Mucosal lesions may occur but are rare. Nail involvement can also occur and may be the only presenting sign in those with minimal phenotypic expression. Overall prognosis is good, with cosmesis of scars being the most troublesome sequela for patients. RDEB has recently been reclassified into RDEB-severe generalized and RDEB-other.16,23 RDEB-severe generalized was previously known as Hallopeau-Siemens subtype. Blisters typically occur at birth and continue to occur with trauma as well as spontaneously, most commonly on bony prominences. Scarring, pigmentation alteration, and milia are common. Scarring of the hands is most severe, leading to mitten deformities and contractures. Oral and upper gastrointestinal strictures can cause serious nutritional abnormalities and growth disturbances. These patients have a significantly increased risk of squamous cell carcinoma, and cutaneous malignancy among these conditions may require dermatologic evaluation to rule out any other underlying disorders. Blisters may also be due to infectious etiologies. Pediatricians and dermatologists should be familiar with clinical presentations of various infectious dermatoses. Obtaining a thorough maternal and perinatal history is essential for timely diagnosis and initiation of treatment. Blisters may be the first clue to the presence of an inherited disorder. It is important to diagnose these conditions due to the many associated extracutaneous manifestations.

This review addresses various causes of blisters in the newborn, but it is certainly not a comprehensive list of all potential causes of blisters in the newborn. There is wide variability in clinical presentation amongst each of these disorders. Therefore, a high index of clinical suspicion may substantiate performing a biopsy and any other necessary testing in order to diagnose these newborns in a timely fashion, work them up for any associated abnormalities, and treat them appropriately.

**References**


**CONCLUSION**

Blisters in the newborn can be a cause of anxiety and concern for parents and physicians as well. Often, the blisters are part of benign, physiologic, and transient changes commonly seen in the newborn. These eruptions are not frequently encountered by the dermatologist as the parents are typically reassured by the pediatrician, who is quite familiar with these eruptions. Persistent and unusual variants of these eruptions may require dermatologic evaluation to rule out any other underlying disorders. Blisters may also be due to infectious etiologies. Pediatricians and dermatologists should be familiar with clinical presentations of various infectious dermatoses. Obtaining a thorough maternal and perinatal history is essential for timely diagnosis and initiation of treatment. Blisters may be the first clue to the presence of an inherited disorder. It is important to diagnose these conditions due to the many associated extracutaneous manifestations.

This review addresses various causes of blisters in the newborn, but it is certainly not a comprehensive list of all potential causes of blisters in the newborn. There is wide variability in clinical presentation amongst each of these disorders. Therefore, a high index of clinical suspicion may substantiate performing a biopsy and any other necessary testing in order to diagnose these newborns in a timely fashion, work them up for any associated abnormalities, and treat them appropriately.
Table 1
Epidermolysis Bullosa Variants

<table>
<thead>
<tr>
<th></th>
<th>Mode of Inheritance</th>
<th>Genetic Defect/ Cleavage Plane</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EBS: Weber –Cockayne</strong></td>
<td>Autosomal Dominant</td>
<td>Keratins 5/14 Intraepidermal</td>
<td>1. Localized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Palms, soles</td>
</tr>
<tr>
<td><strong>EBS: Koebner</strong></td>
<td>Autosomal Dominant</td>
<td>Keratins 5/14 Intraepidermal</td>
<td>3. Generalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Palms, soles, over joints and areas of trauma</td>
</tr>
<tr>
<td><strong>EBS: Dowling-Meara</strong></td>
<td>Autosomal Dominant</td>
<td>Keratins 5/14 Intraepidermal</td>
<td>5. Generalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6. Herpetiform</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7. Mucosa, nail involvement</td>
</tr>
<tr>
<td><strong>EBS: EB with Muscular Dystrophy</strong></td>
<td>Autosomal Recessive</td>
<td>Plectin Hemidesmosome</td>
<td>1. Generalized</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2. Late onset muscle abnormalities</td>
</tr>
<tr>
<td><strong>JEB: Herlitz</strong></td>
<td>Autosomal Recessive</td>
<td>Laminin 332 Intralamina lucida</td>
<td>1. Beefy red periorificial granulation tissue</td>
</tr>
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<td></td>
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<td>2. Poor prognosis</td>
</tr>
<tr>
<td><strong>JEB: Non-Herlitz</strong></td>
<td>Autosomal Recessive</td>
<td>Laminin 332 BP Ag 1 BP Ag 2 Intralamina lucida</td>
<td>3. Normal lifespan</td>
</tr>
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<td><strong>DEB: Dominant</strong></td>
<td>Autosomal Dominant</td>
<td>Collagen 7 Sublamina densa</td>
<td>4. Clinical variability</td>
</tr>
<tr>
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<td>5. Good prognosis</td>
</tr>
<tr>
<td><strong>DEB: Recessive</strong></td>
<td>Autosomal Recessive</td>
<td>Collagen 7 Sublamina densa</td>
<td>6. Mitten deformity</td>
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<td>7. Mortality from cutaneous malignancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8. Poor prognosis</td>
</tr>
</tbody>
</table>

**Figure 1**
Eccrine apparatus

**Figure 2**
Evolution of Incontinentia Pigmenti

- **Inflammatory Phase**
- **Verrucous Phase**
- **Hyperpigmentation**
- **Hypopigmentation**
**Granulomatous Rosacea: A Case Report and Literature Review**

*3rd-year dermatology resident, Northeast Regional Medical Center/Kirksville College of Osteopathic Medicine, Department of Dermatology, Texas Division, Duncanville, Texas**  
**Traditional intern, University Hospitals Richmond Medical Center, Richmond Heights, Ohio**  
***Program Director, Northeast Regional Medical Center/Kirksville College of Osteopathic Medicine, Department of Dermatology, Texas Division, Duncanville, Texas

**ABSTRACT**

We describe the clinical features of granulomatous rosacea (GR) of the eyelids. GR is classified as a variant of rosacea. Histologically the lesions show caseating and more commonly, noncaseating granulomas that may mimic other diseases such as tuberculosis, sarcoidosis and leprosy. GR has been reported in children, adults and in association with HIV.

**Case Report**

An otherwise healthy, 2-year-old Hispanic male presented to the clinic with a one-month history of itchy, red, elevated lesions bilaterally on the medial lower eyelids. The patient's mother denied any history of a similar rash and admitted to trying oral amoxicillin and gentamicin eye drops without success. Review of systems was negative, and the past medical history was insignificant. Initial physical examination showed a 20 mm, linear, red, scaly, indurated plaque with yellow crust on the right inferior eyelid. The left inferior eyelid had a similar-appearing lesion measuring 15 mm (Figure 1). Per their pediatric ophthalmologist, the eye exam was normal. Bacterial cultures and sensitivities were ordered, and the patient was started empirically on oral erythromycin syrup and Neosporin ophthalmic ointment.

Weeks later, the lesions remained with no improvement, and exudate was noted (Figure 2). Bacterial cultures grew Moraxella catarrhalis with beta lactamase positivity. Azithromycin was started, and Neosporin ophthalmic drops were switched to bacitracin ophthalmic ointment with warm eye compresses. Months later, the patient had mild improvement, with decreased erythema and inflammation. Hair loss and three 2 mm erythematous papules on the right cheek also appeared. A shave biopsy of the left lower eyelid was performed. The final diagnosis showed mixed lymphoplasmacytic and granulomatous dermatitis, which may be seen in granulomatous rosacea. Our patient's mother was given information regarding this skin condition; however, the patient was lost to follow-up.

Rosacea is a cutaneous disorder that primarily involves the cheeks, nose, chin, forehead, and ears.1-4 It is a chronic inflammatory disorder of the skin that affects the face. Rosacea is characterized by redness, flushing, and inflammation. Secondary signs include: telangiectasia, papules/pustules/nodules, and telangiectasia. The presence of at least one primary sign indicates rosacea. Secondary signs used to support primary features, include: burning, stinging, dryness, plaques, ocular manifestations (chalazion or hordeolum are common presentations), and phymatous changes (occurring on the nose, chin, forehead, cheeks, and ears).5-6 In 2002, the National Rosacea Society defined four rosacea subtypes: erythematous, telangiectatic, papulopustular, phymatous, ocular; and one variant, GR. The most common patterns of primary and secondary signs are used to define the various subtypes. Although part of the rosacea spectrum, GR is classified as a variant of rosacea due to its unique histopathological findings.3,5,6

Clinically, GR is described as a painless eruption of red, reddish to yellow-brown papules or nodules of uniform size.7-10 Lesions tend to have less inflammation than the papules or pustules seen in the rosacea subtypes. The cheeks and perioral area are most commonly involved; however, perioral involvement has been reported.1,4,6-9 GR typically affects adolescents, middle-aged women and immunosuppressed patients.8,9 Primary and secondary signs of rosacea are not required to diagnose granulomatous rosacea.2-5 Rather, the diagnosis is dependent upon the histological identification of a granulomatous infiltrate, usually noncaseating granulomas, which may be centered on a ruptured hair follicle.11-14 Caseating granulomas may be present in 10-20% of cases.8

Within the GR variant, four histopathological patterns have been described: nodular, perifollicular, diffuse, and combined perifollicular/nodular. The nodular pattern has both deep and superficial lymphocytic and histiocytic infiltrates, with plasma cells appearing in some cases. Lymphocytes are the predominant cells seen in the perifollicular pattern. The diffuse pattern is classified by lymphocytes and histiocytes seen primarily within the reticular dermis. Finally, the combined nodular/perifollicular pattern consists of lymphocytes mixed with neutrophils and occasional multinucleated giant cells and/or plasma cells.7

The pathogenesis of GR is a well-debated subject. Causative factors include: sun exposure resulting in damage to the dermal matrix, pilosebaceous unit inflammation secondary to follicular based organisms (Propionibacterium acnes/Demodex folliculorum), and microbial organisms (Demodex folliculorum, Demodex brevis and Helicobacter pylori).1,2,6-9 The noncaseating granulomas have been suggested to represent a foreign-body reaction against keratinized cells from pilosebaceous units or a delayed hypersensitivity reaction to D. folliculorum.6 Sanchez1 reported 24 cases of GR with only seven of the biopsies showing Demodex folliculorum. However, in all seven cases, the mite was either within the granulomas or within follicles surrounded by granulomas. This association of the mite within and around granulomas supports the idea that Demodex folliculorum may stimulate an inflammatory reaction that manifests as rosacea. Regardless of the cause, GR is a variant of rosacea and requires histological evidence for the diagnosis.

According to the National Rosacea Society, GR is a variant of rosacea with a unique clinical appearance that does not require other rosacea signs for diagnosis.7 GR can have a wide variety of clinical presentations and is best thought of as a histological variant, rather than a disease variant, seen within one of the subtypes of rosacea.1 If GR is identified in patients who have a clinical diagnosis of rosacea, then we have to consider the diagnosis of ocular rosacea in our patient. Ocular rosacea can be diagnosed when one or more of the following ocular symptoms are present: telangiectasias of the sclera or other parts of the eye, periocular erythema, foreign-body sensation, burning or stinging, dryness, itching and ocular photosensitivity.1 In one study that
looked at 20 children with rosacea (mean age at presentation was 4.2 years old), the most common ocular manifestations in cases involving the eyes were meibomian gland inflammation (chalazion) and ocular hyperemia. Ocular symptoms of burning, stinging and chalazions usually precede cutaneous signs; however, studies have reported concurrent presentations of ocular and facial rosacea. Ocular rosacea leads to dysfunctional meibomian glands that produce thickened secretions and hypertrophic eyelid margins. Meibomian-gland dysfunction may occur secondary to increased facial temperatures seen with the vasodilatation of rosacea or may be associated with abnormal amounts of glandular secretions due to bacterial lipases. Although tetracycline and minocycline have shown good results in ocular rosacea, the use of tetracyclines in children is contraindicated. Metronidazole has been effective in children. For ocular rosacea, topical erythromycin or metronidazole ophthalmic gel in conjunction with good eye hygiene and warm compresses is recommended.

**Conclusion**

We presented the case of a 2-year-old male with granulomatous rosacea. Due to his age and lack of communication, we were unable to assess whether the burning, itching and foreign body sensations of ocular rosacea were indeed present. The painless papules, periorbital involvement and histological findings of a granulomatous infiltrate associated with a ruptured follicle are all consistent with the diagnosis of granulomatous rosacea. Regardless of the classification, any child suspected of having rosacea should be referred to an ophthalmologist. Early detection of ocular involvement can help prevent the complications of ocular rosacea, including keratitis, scleritis, iritis and corneal ulcerations.

**References**

**A BRIEF REVIEW OF LEUKONYCHIA**

Albert E. Rivera, DO,* Lloyd J. Cleaver, DO**  
*Dermatology Resident, Third Year, Northeast Regional Medical Center, Kirksville, Missouri  
**Program Director, Dermatology, Northeast Regional Medical Center, Kirksville, Missouri

**ABSTRACT**

Leukonychia, by definition, is a whitening or apparent whitening of the nails and is the most common nail-color variant.1 The knowledge and classification of this condition have both progressed over the years. Lawrence reported in 1893 that leukonychia could have a hereditary component.2 Three years later, Unna developed a classification system for leukonychia that included the categories of punctuate, striate or total.3 In 1918, Weber added a fourth component, incomplete, along with multiple valuable case summaries demonstrating the various types.4 Cockayne added in 1933 that most cases of inherited leukonychia were specifically autosomal dominant.5 Though some have more recently classified leukonychia based on the location of the nail defect,6 the most simple and accepted method is that noted above for “true” leukonychias – punctuate, striate, partial and total – as distinct from apparent or pseudoleukonychia. Figure 1 provides a general outline of each of these categories. The purpose of the following discussion, though it will include all variants, will be primarily to expand on the true leukonychias.

**True Leukonychia**

True leukonychia is caused by diseases or factors that disturb nail-matrix keratinization. The appearance is attributed to light diffraction produced by the parakeratotic cells.7 Often, congenital cases are inherited in either an autosomal-dominant fashion or dominant with varying penetrance.8,9 There are, however, two seemingly idiopathic cases reported (the case by Butterworth reported by others as idiopathic was actually hereditary), most recently in 2001.10,11,12

**Punctate Leukonychia**

The first subset of the true leukonychias, punctuate, is the most common presentation. Many times, this is found in younger individuals. On physical exam, small, 1 to 3 millimeter white spots are found that progress distally with nail growth. Occasionally, they may resolve prior to reaching the distal edge. The most frequent cause of this variant is trauma or nail manipulation (such as a manicure). Interestingly, in psoriasis, when the focus of parakeratosis is within the mid-matrix, it leads to the commonly seen punctate lesions of the nail plate; however, when the parakeratosis is within the proximal matrix, the cells progress to the superficial plate and subsequently fall out, leading to nail pitting.

**Transverse Leukonychia**

Transverse leukonychia is another subtype of the true leukonychias. Presentation is often seen in females as transverse, parallel, 1 to 3 millimeter white lines. Injury to the mitotically active matrical cells is causal. This most commonly results from manipures, nervous tics and shoes. However, multiple etiologies have been reported. Keyboard use, cryotherapy, salt immersion and medications including chemotherapy are causes.13,14 The transverse leukonychia caused by chemotherapy is usually transient and will resolve with stoppage of the inciting treatment.15 A genetic link is also found. Heimer reported a probable autosomal-recessive syndrome found in a brother and sister with sensorineural hearing loss, enamel hypoplasia and nail defects (both transverse and punctuate leukonychia).16 Other documented factors include arsenic intoxication (Mee’s lines), renal failure, liver disease, myocardial infarction, anemia, systemic lupus erythematosus, malnutrition, sickle cell disease, Hodgkin’s disease, acquired immunodeficiency syndrome (AIDS), Hailey-Hailey disease (more so longitudinal),17 Darier’s disease and Kawasaki’s disease.18 Specifically, in one study of renal transplant patients, the most frequent nail pathology observed was leukonychia (at 21.5%).19 Nail findings attributed to arterial spasms secondary to hypocalcemia have also been seen.20 Infectious diseases, specifically respiratory illness, measles, malaria, tuberculosis, pleural empyema, herpes zoster and leprosy, have all been associated as well.21

**Partial Leukonychia**

The next category within the true leukonychias is partial (or diffuse) leukonychia. This is more rarely reported and has been postulated by some to possess a hereditary component. Giustina reported an 18-year-old female with apparent autosomal-dominant congenital partial leukonychia associated with pili torti.22 In contrast, others report individual cases related to increased blood strontium or hydroxyurea rather than to genetic factors.23,24 It is even proposed that partial leukonychia is a component phase of leukonychia totalis rather than a distinct category since progression to such has been reported to occur.21,23

**Leukonychia Totalis**

Leukonychia totalis (Figure 2) is the last of the true leukonychias to be discussed and is very uncommon. In 1950, there had been 55 cases reported. Interestingly, as recent as that period, hereditary presentations were considered a “purely ‘cosmetic’ defect and of academic interest only.”26 By 1982, there were approximately 100 hereditary events that had been discussed. Some of the hereditary cases include ectodermal dysplasias, while others are seemingly without additional findings.27-29 Most often, these hereditary cases are characterized as autosomal-dominant, though one report of apparent autosomal-recessive inheritance is found.30 An excellent work by Morin et al. charts several syndromic conditions which have been associated with leukonychia as well as other occasional exam findings present with leukonychia.31 These will be expanded upon forthcoming. Over time, leukonychia totalis has also been found to be acquired with the development of systemic conditions such as cirrhosis, congestive heart failure, hypoalbuminemia, renal failure, diabetes mellitus, reflex sympathetic dystrophy, human immunodeficiency virus (HIV) and Hodgkin’s lymphoma.32-34 Figure 3 presents an overview of both the syndromic and associated conditions.

**Syndromic Conditions**

Bauer syndrome is an autosomal-dominant condition which presents with sebaceous cysts and leukonychia.35 Bushkell and Gorlin reported five individuals over four generations with similar findings of leukonychia and multiple sebaceous cysts but who also had renal calculi.36,37 In addition to the leukonychia totalis and sebaceous cysts, ciliary dystrophy (leading to conjunctival irritation and watering) was proposed as part of the FLOTCH (Familial LeucOnychia, Trichilemmal cysts, Ciliary dystrophy, autosomal dominantly inherited) syndrome modification.59 Most recently, in 1997, a possible variant association with pancreatitis was also questioned.39

Knuckle pads (and likely plantar keratoderma), mixed sensorineural and conductive hearing loss in association with leukonychia totalis describes the autosomal-dominant triad of Bart-Pumphrey syndrome.40,41 A missense mutation of GJB2 (gap junction protein, beta 2) with possible variable expressivity is causal.42 Vohwinkel’s syndrome has incorrectly been reported...
to include leukonychia. However, the initial classification of this disorder included constrictions of the fingers, keratoderma and congenital deafness with no inclusion of nail findings. 43 Hooft syndrome is a likely autosomal-dominant recessive constellation of total leukonychia, mental retardation, erythematousquamous eruption, low serum lipids and tapetoretinal degeneration. 44

**Summary**

As demonstrated, leukonychia consists of several subtypes as well as etiologies. Since it is the most common nail color variant, there are multiple known genetic, internal and external factors that may be related. Also, the frequency at which it is seen leads to multiple disorders that may possibly include its presence as a diagnostic criterion. The purpose of this work is not to elaborate and expand on all of the subtypes of leukonychia, but to group a majority of the causes and conditions together in one location from which the reader can then let their interest direct them. Further, detailed information on any of the conditions noted may be researched using the references cited as a point to begin the search. Future reports on patients with leukonychia as well as new technologies (such as genetic testing) should support a clearer understanding and classification of this common oil finding.

**References**

Figure 1: Most Common Causes of Leukonychia

I. True Leukonychia
   a. Punctate
      i. Traumatic
      ii. Immunologic (Psoriasis)
   b. Transverse
      i. Traumatic
      ii. Chemical/Medication
      iii. Genetic
      iv. Organ Disease
      v. Connective Tissue Disease
      vi. Nutritional
      vii. Infectious
      viii. Immunodeficiency
   c. Partial/Diffuse
      i. Genetic
      ii. Chemical/Medication
   d. Totalis
      i. Genetic
      ii. Organ Disease
      iii. Immunologic
      iv. Nutritional
      v. Syndromic/Medically Associated

II. Apparent Leukonychia
   i. Chemical/Medication
   ii. Organ Disease
   iii. Nutritional
   iv. Age

III. Pseudoleukonychia
   i. Infectious (Fungal)
   ii. Topicals

<table>
<thead>
<tr>
<th>Leukonychia Totalis Syndromes</th>
<th>Leukonychia Totalis Associations</th>
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<tbody>
<tr>
<td><strong>Bauer Syndrome</strong></td>
<td>Yamamoto</td>
</tr>
<tr>
<td>Leukonychia Totalis</td>
<td>Leukonychia Totalis</td>
</tr>
<tr>
<td>Sebaceous Cysts</td>
<td>Multiple Epiphyseal Dysplasia</td>
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<tr>
<td></td>
<td>Mild Short Stature</td>
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<tr>
<td></td>
<td>Small Head</td>
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<tr>
<td></td>
<td>Mental Retardation</td>
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<tr>
<td></td>
<td>Congenital Nystagmus</td>
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<tr>
<td></td>
<td>Hypoplasia of the Corpus Callosum</td>
</tr>
<tr>
<td><strong>Bauer Syndrome (Buskell-Gorlin variant)</strong></td>
<td>Ingegno (All Variably Present)</td>
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<td>Leukonychia Totalis</td>
<td>Leukonychia Totalis</td>
</tr>
<tr>
<td>Sebaceous Cysts</td>
<td>Duodenal Ulcers</td>
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<td></td>
<td>Gallstones</td>
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<tr>
<td><strong>FLOTCH Syndrome</strong></td>
<td>Basaran</td>
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<tr>
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<td>Leukonychia Totalis</td>
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<tr>
<td>Sebaceous Cysts</td>
<td>Hypotrichosis (Trichorrhexis Nodosa and</td>
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<td>Giliary Dystrophy</td>
<td>Trichoptilosis)</td>
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<td>Autosomal Dominant</td>
<td>Xerosis</td>
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<tr>
<td></td>
<td>Transgrediens Palmoplantar Keratoderma</td>
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<td></td>
<td>Hyperkeratosis of the Knees, Elbows and</td>
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<tr>
<td></td>
<td>Perianal Areas</td>
</tr>
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<td><strong>Bart-Pumphrey Syndrome</strong></td>
<td>Galadari</td>
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<td>Leukonychia Totalis</td>
<td>Leukonychia Totalis</td>
</tr>
<tr>
<td>Knuckle Pads</td>
<td>Keratosis Pilaris</td>
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<tr>
<td>Mixed Sensorineural and Conductive</td>
<td>Hyperhidrosis</td>
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<tr>
<td>Hearing Loss</td>
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<td>Autosomal Dominant</td>
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<tr>
<td><strong>Hooft Syndrome</strong></td>
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<td>Leukonychia Totalis</td>
<td>Leukonychia (Total and Partial)</td>
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<tr>
<td>Mental Retardation</td>
<td>Axonal Neuropathy</td>
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<td>Erythematousquamous Eruption</td>
<td>Muscular Dystrophy</td>
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<td>Low Serum Lipids</td>
<td>Cardiac Disease</td>
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<td>Tapetoretinal Degeneration</td>
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<tr>
<td>Isolated Congenital Leukonychia Totalis</td>
<td>Isolated Congenital Leukonychia Totalis</td>
</tr>
</tbody>
</table>

Figure 3
ZIANA Gel is specifically designed with tolerability in mind.¹

- Indicated for the topical treatment of acne vulgaris in patients 12 years or older.
- Suspended crystalline tretinoin in vehicle designed to deliver the active ingredients to the skin.²
- Hydrogel alcohol-free aqueous base.¹

Important Safety Information for ZIANA Gel

- The most commonly reported adverse events were nasopharyngitis, pharyngolaryngeal pain, dry skin, cough, and sinusitis.
- Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical clindamycin. ZIANA Gel should be discontinued if significant diarrhea occurs. Systemic absorption of clindamycin has been demonstrated following topical use of this product.
- If a reaction suggesting sensitivity or chemical irritation occurs, use of the medication should be discontinued.
- Avoid exposure to sunlight and sunlamps. Patients with sunburn should not use the product. Use with caution in patients who require considerable sun exposure due to occupation or who are inherently sensitive to the sun. Avoid excessive exposure to the sun, cold, and wind, which can irritate skin. Daily use of sunscreen and protective clothing are recommended.
- Keep away from eyes, mouth, angles of nose, and mucous membranes.
- This drug is contraindicated in patients with regional enteritis, ulcerative colitis, or history of antibiotic-associated colitis.
- Concomitant use of topical medications with a strong drying effect can increase skin irritation. Use with caution.

See reverse side for a Brief Summary of the Full Prescribing Information.

2. NDA 50-802 for ZIANA Gel; Sections 4.4.4.1 & 4.2.5. 2006. Data on file, Medicis Pharmaceutical Corporation.
the colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may
studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis.
several weeks following cessation of therapy. antiperistaltic agents such as opiates and diphenoxylate
in the 12-week studies. eight out of 442 subjects (4%) reported gastrointestinal symptoms.
related to drug use for approximating rates.
Clinical Studies Experience
Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the
antibiotic-associated colitis.
Ziana® Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of
Ziana® Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.
For topical use only
Ziana® Gel is a registered trademark of Medicis pharmaceutical corporation.
u.s. patents 5,721,275 and 6,387,383
scottsdale, arizona 85256
Medicis, the Dermatology company
BRIEF SUMMARY
RX ONLY
FOR TOPICAL USE ONLY
INDICATIONS AND USAGE
ZIANA® Gel is indicated for the topical treatment of acne vulgaris in patients 12 years or older.
CONTRAINDICATIONS
ZIANA® Gel is contraindicated in patients with regional enteritis, ulcerative colitis, or history of
antibiotic-associated colitis.
WARNINGS AND PRECAUTIONS
Systemic absorption of clindamycin has been demonstrated following topical use of this product.
Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the
use of topical clindamycin. When significant diarrhea occurs, ZIANA® Gel should be discontinued.
Severe colitis has occurred following oral or parenteral administration of clindamycin with an onset of up
several weeks following cessation of therapy. Antiperistaltic agents such as opiates and diphenoxylate
with atropine may prolong and/or worsen severe colitis. Severe colitis may result in death.
Studies indicate a toxin(s) produced by clostridia is one primary cause of antibiotic-associated colitis.
The colitis is usually characterized by severe persistent diarrhea and severe abdominal cramps and may
be associated with the passage of blood and mucus. Stool cultures for Clostridium difficile and stool
assay for C. difficile toxin may be helpful diagnostically.
Ultraviolet Light and Environmental Exposure
Exposure to sunlight, including suntamps, should be avoided during the use of ZIANA® Gel, and patients
with sunburn should be advised not to use the product until fully recovered because of heightened
susceptibility to sunlight as a result of the use of tretinoin. Patients who may be required to have
considerable sun exposure due to occupation and those with inherent sensitivity to the sun should
exercise particular caution. Daily use of sunscreen products and protective apparel (e.g., a hat) are
recommended. Weather extremes, such as wind or cold, also may be irritating to patients under
treatment with ZIANA® Gel.
ADVERSE REACTIONS
Clinical Studies Experience
Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in
clinical trials may not reflect the rates observed in practice. The adverse reaction information from
clinical trials does, however, provide a basis for identifying the adverse reactions that appear to be
related to drug use for approximating rates.
The safety data presented in Table 1 (below) reflects exposure to ZIANA® Gel in 1,853 patients with acne
vulgaris. Patients were 12 years and older and were treated once daily for 12 weeks. Adverse reactions
that were reported in ≥ 1% of patients treated with ZIANA® Gel were compared to adverse reactions in
patients treated with clindamycin phosphate 1.2% in vehicle gel, tretinoin 0.025% in vehicle gel, and the
vehicle gel alone:

<table>
<thead>
<tr>
<th>Table 1: Adverse Reactions Reported in at least 1% of Patients Treated with ZIANA® Gel: 12-Week Studies</th>
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<tbody>
<tr>
<td><strong>ZIANA® Gel</strong></td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
</tr>
<tr>
<td>91 (22)</td>
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<tr>
<td>23 (1)</td>
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<tr>
<td>21 (2)</td>
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<tr>
<td>19 (1)</td>
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<tr>
<td>15 (2)</td>
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<tr>
<td>237 (13)</td>
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<tr>
<td>189 (10)</td>
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<tr>
<td>38 (2)</td>
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<td>33 (2)</td>
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</tbody>
</table>

Cutaneous safety and tolerance evaluations were conducted at each study visit in all of the clinical trials
by assessment of erythema, scaling, itching, burning, and stinging:

<table>
<thead>
<tr>
<th>Table 2: ZIANA® Gel-Treated Patients with Local Skin Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Reaction</strong></td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
</tr>
<tr>
<td>Erythema</td>
</tr>
<tr>
<td>Scaling</td>
</tr>
<tr>
<td>Itching</td>
</tr>
<tr>
<td>Burning</td>
</tr>
<tr>
<td>Stinging</td>
</tr>
</tbody>
</table>

At each study visit, application site reactions on a scale of 0 (none), 1 (mild), 2 (moderate), and 3
(severe), and the mean scores were calculated for each of the local skin reactions. In Studies 1 and
2, 1,277 subjects enrolled with moderate to severe acne. 854 subjects treated with ZIANA® Gel and
423 treated with vehicle. Analysis over the twelve week period demonstrated that cutaneous irritation
scores for erythema, scaling, itching, burning, and stinging peaked at two weeks of therapy, and were
slightly higher for the ZIANA®-treated group, decreasing thereafter.

One open-label 12-month safety study for ZIANA® Gel showed a similar adverse reaction profile as seen
in the 12-week studies. Eighteen out of 442 subjects (4%) reported gastrointestinal symptoms.

DRUG INTERACTIONS
Concomitant Topical Medication
Concomitant topical medication, including soaps and cleansers, and cosmetics that have a strong drying
effect, and products with high concentrations of alcohol, astringents, spices or lime should be used with caution. When used with ZIANA® Gel, there may be increased skin irritation.

Erythromycin
ZIANA® Gel should not be used in combination with erythromycin-containing products due to its
c tinamycin component. In vitro studies have shown antagonism between these two antimicrobials. The
clinical significance of this in vitro antagonism is not known.

Neuromuscular Blocking Agents
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action
of other neuromuscular blocking agents. Therefore, ZIANA® Gel should be used with caution in patients
receiving such agents.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. There are no well-controlled trials in pregnant women treated with ZIANA® Gel. ZIANA® Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ZIANA® Gel was tested for maternal and developmental toxicity in New Zealand White Rabbits with topical doses of 60, 180 and 600 mg/kg/day. ZIANA® Gel at 600 mg/kg/day (approximately 12 times the recommended clinical dose assuming 100% absorption and based on body surface area comparison) was considered to be the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity following dermal administration of ZIANA® Gel for two weeks prior to artificial insemination and continuing until gestation day 18, inclusive. For purposes of comparisons of the animal exposure to human exposure, the recommended clinical dose is defined as 1 g of ZIANA® Gel applied daily to a 60 kg person.

Clindamycin
Teratology (Segment II) studies using clindamycin were performed orally in rats (up to 600 mg/kg/ day) and mice (up to 100 mg/kg/day) (583 and 49 times amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) or with subcutaneous doses of clindamycin of up to 180 mg/kg/day (175 and 88 times the amount of clindamycin in the recommended clinical dose based on a body surface area comparison, respectively) revealed no evidence of teratogenicity.

Tretinoin
In oral Segment III studies in rats with tretinoin, decreased survival of neonates and growth retardation
were observed at doses in excess of 2 mg/kg/day (78 times the recommended clinical dose assuming
100% absorption and based on body surface area comparison).

With widespread use of any drug, a small number of birth defect reports associated temporally
with the administration of the drug would be expected by chance alone. Thirty cases of temporally
associated congenital malformations have been reported during two decades of clinical use of another
formulation of topical tretinoin. Although no definite pattern of teratogenicity and no causal association
have been established from these cases, 5 of the reports describe the rare birth defect category,
holoprosencephaly (defects associated with incomplete midline development of the forebrain).
The significance of these spontaneous reports in terms of risk to the fetus is not known.

Dermal tretinoin has been shown to be fetotoxic in rabbits when administered in doses 40 times the
recommended human clinical dose based on a body surface area comparison. Oral tretinoin has been shown
to be fetotoxic in rats when administered in doses 78 times the recommended clinical dose based on
a body surface area comparison.

Nursing Mothers
It is not known whether clindamycin is excreted in human milk following use of ZIANA® Gel. However,
oral and parenterally administered clindamycin has been reported to appear in breast milk. Because
of the potential for serious adverse reactions in nursing infants, 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. It is not known whether tretinoin is excreted in human milk. Because many drugs are excreted
in human milk, caution should be exercised when ZIANA® Gel is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of ZIANA® Gel in pediatric patients under the age of 12 have not been
established.

Clinical trials of ZIANA® Gel included patients 12–17 years of age.

Geriatric Use
Clinical studies of ZIANA® Gel did not include sufficient numbers of subjects aged 65 and over to
determine whether they respond differently from younger subjects.

Manufactured for:
Medicis, The Dermatology Company
Scottsdale, AZ 85256
U.S. Patents 5,721,275 and 6,387,383
ZIANA is a registered trademark of Medicis Pharmaceutical Corporation.
Prescribing Information as of October 2008.
300-138
**Ontology or Not to Biopsy: Simple and Practical Dermoscopy**

**A Practical Dermosscopic Approach to Manage Pigmented Lesions**

Hamza Bhatti, OMSIV,* Omar Noor, MSIV,** Babar K. Rao, MD***
*Touro College of Osteopathic Medicine, New York, New York
**George Washington University School of Medicine and Health Sciences, Washington, DC
***Associate Professor, Department of Dermatology, UMDNJ – Robert Wood Johnson Medical School, New Brunswick, New Jersey

**ABSTRACT**

Our approach to managing pigmented lesions focuses upon whether to biopsy or not, rather than labeling it benign or malignant. This is based upon recognizing common patterns requiring no biopsy, seen in benign pigmented lesions, i.e., a patchy network, homogeneous, homogenous brown, reticular, and reticulo-globular patterns. Conversely, lesions with known suspicious or atypical patterns such as a blue-white veil, atypical pigment network, multiple colors, regression, leaf-like structures, irregular streaks and/or unknown patterns require biopsy. This allows clinicians to utilize dermoscopy more effectively in their practices.

**Objective**

To devise an uncomplicated system to allow novice dermatologists to efficiently use dermoscopy in their practices.

**Background**

Dermoscopy (also known as dermatoscopy, epiluminescence microscopy, skin surface microscopy, and incident light microscopy) aids physicians in the early diagnosis of malignant melanoma by allowing a more detailed view of cutaneous lesions than with the naked eye. While skin normally appears opaque, thus hindering inspection of underlying structures, dermoscopy enables physicians to better visualize structures underneath the stratum corneum and has been shown to increase diagnostic accuracy for malignant melanoma and other pigmented skin lesions. A 2002 melanoma detection study by Bono et al. found that combining dermoscopy with clinical evaluation achieved a sensitivity of 97% compared to 86% with clinical evaluation alone.

Dermoscopy is becoming more popular as an aid for diagnosing pigmented lesions, but it is still in its infancy. As of 2005, only 17.4% in a survey of 1,200 randomly selected U.S. dermatologists use dermoscopy in clinical assessment of melanoma in situ. We believe this low prevalence of usage is due in part to the complexity of commonly used dermoscopy algorithms. A recent survey of dermatology residents in training concluded that 51% of respondents use dermoscopy, and that 45% anticipate a dramatic increase in use over the next five years.

Though the majority of American dermatologists do not use dermoscopy as a diagnostic tool, dermoscopy is cost effective, leads to a decreased number of excised benign lesions, and allows the early detection of melanoma. Most available dermoscopic algorithms focus on distinguishing benign lesions from malignant ones, which may not be possible or practical in all cases. These algorithms, when used by experienced dermatologists, are very effective at diagnosing skin cancer, but when used by non-experienced dermatologists, the effectiveness drops considerably. Thus, we have devised a simplified approach to dermoscopy which is easy, does not depend on vast past experience, and has proven useful in determining which lesions need to be biopsied.

**Introduction**

Much dermoscopy research and teaching has been focused on defining dermoscopic criteria. These definitions are the foundation on which our Simple and Practical Dermoscopy (SPD) technique is based. Past methods have used these criteria when analyzing a lesion and entered them into algorithms, including the ABCD method, Menzies scoring method, 7-point checklist, and pattern analysis, all of which have been validated as aids in clinical assessment of pigmented lesions. However, due to the complexity of some of these algorithms and their time-consuming nature, dermoscopy use in the U.S. has been largely the task of academic dermatologists for research purposes rather than a source in community practices where the majority of patient visits occur. It is not surprising, therefore, that newer and simpler algorithms, such as the three-point checklist and the CASH method, have been created and validated in an attempt to broaden the use of dermoscopy.

**Methods**

Our approach (SPD) to a pigmented lesion is based upon two simple questions:

1) Does the lesion have a known or unknown pattern? and
2) Are there any suspicious features?

Simply put, if a lesion has a known, benign pattern, without suspicious features, a biopsy is often unnecessary. However, if the pattern is unknown or if the lesion has suspicious features, it should be removed. In order to explain our approach, first we describe criteria for melanocytic neoplasms, common known features of benign pigmented lesions; then features of non-melanocytic lesions; and then the suspicious features of pigmented lesions. Experienced clinicians in dermoscopy do not need the following explanation; however, for beginners, the dermoscopic criteria for melanocytic and non-melanocytic lesions are described.

**Known Dermoscopic Patterns of Melanocytic Neoplasms:**

A melanocytic neoplasm usually contains a pigmented network (Figures 1 & 2) and/or globules (Figures 3 & 4). There are several known dermoscopic configurations of benign melanocytic nevi. Although we don’t need to categorize various pigmented lesions as nevi, seborrheic keratoses, or basal cell carcinoma for our approach, it is explained for better understanding of how dermoscopic observations correlate with naked eye examinations and with history.

Nevi can have a reticular network pattern, which is found in both junctional and dysplastic nevi (Figures 1 & 2). Pigmented networks are a grid of brown lines over a diffuse, light-brown background in pigmented lesions. The networks can be further categorized into two subgroups, atypical and typical. Typical pigmented networks are composed of a meshed network evenly distributed throughout the periphery of the lesion. There may be either a diffuse or abundance of network in the center or periphery of the pigmented lesion. The patterns are consistent with known benign patterns and therefore do not need to be biopsied. An atypical pigment network consists of black or gray network with irregular meshes and thick lines. It can also contain streaks, which are irregular linear structures not clearly combined with pigment network lines. These features lead a clinician in the direction of biopsy, ultimately having a higher likelihood of melanoma.

A reticulo-globular pattern is frequently found in compound or dysplastic nevi. Globular-only patterns are common in intradermal and congenital nevi and consist of dots and globules. These dots and globules are round structures varying in size and are usually brown, gray, or black. Dots and globules can also be further divided into two categories, regular and irregular. A regular pattern is identified as dots and globules of the same size that are uniformly dispersed in the pigmented lesion. These are benign...
characteristics that indicate that the lesion does not need to be biopsied. If there is a discrepancy in size and/or distribution, this would warrant a biopsy for further evaluation.

A nevus with a homogeneous, brown color network is likely junctional, congenital or dysplastic. Blue nevi have a homogeneous blue pattern, while Spitz/Reed nevi are distinguished by their striking starburst pattern, which is characterized by pigmented streaks symmetrically distributed at the periphery. Spitz/Reed nevi are a slight exception to the rule, as they can range from the completely benign to the rare malignant melanoma.

Additionally, dysplastic nevi have several central or peripheral variants upon the basic reticular or reticulогlobular pattern. These variations include hyperpigmentation or hypopigmentation, central hyperpigmentation or hypopigmentation, patchy hyperpigmentation and/or hypopigmentation, patchy network, and/or peripheral globules. A peripheral or central hyperpigmented or hypopigmented lesion contains a darker or reduced pigment on the peripheral border or center of the lesion, respectively. These patterns are typical of dysplastic nevi and do not need to be biopsied. The most common reason to biopsy a lesion on clinical examination alone is based on pigment variation. Pigment variation is based on the notion that a lesion has a darker or lighter (reduced) color in the central or peripheral areas. These deviations are commonly seen as peripheral or central hyperpigmentation or hypopigmentation, which under dermoscope show no atypical features. These changes in pigment densities help to differentiate between typical and atypical networks.

Known Dermoscopic Patterns of Non-melanocytic Neoplasms

Known non-melanocytic pigmented lesions that may be difficult to manage without dermoscopy include seborrheic keratoses, lentigines, pigmented basal cell carcinomas, hemangiomas, and dermatofibromas. Seborrheic keratoses have features such as multiple milia-like cysts, comedo-like openings, fissures, network-like structures (honeycomb network), fingerprint-like structures, sharply demarcated and/or moth-eaten borders, and crypts. Milia-like cysts are white, round structures found in pigmented lesions that can vary in size. This characteristic is very common in pigmented lesions, and a biopsy is not warranted due to its benign, normal nature. Comedo-like openings vary between brown-yellowish and brown-black with irregularly shaped structures in a pigmented lesion. Comedo-like openings are also considered a known, benign characteristic and do not need to be biopsied.

Basal cell carcinomas are recognized by the absence of a pigmented network along with one or more of the following: arborizing streaks or slits, leaf-like areas, large blue-grey ovoid nests, multiple blue-gray globules, or spoke wheel areas. Pigmented basal cell carcinomas can be difficult to distinguish clinically from melanoma, but dermoscopy has proven to be useful in the differential diagnosis of the two tumour types.

Hemangiomas are distinguished by their red-blue lacunae or red-blue to red-black, diffuse homogeneous areas, and dermatofibromas typically contain a central hypopigmented area and a peripheral network.

Known Patterns of Atypical Pigmented Lesions

There are certain patterns common to melanoma that, when found in a pigmented lesion, warrant a biopsy regardless of the presence of aforementioned characteristics. These features include a blue-white veil, atypical pigmentation network, irregular pigmentation, multiple (five or more) colors, regression, irregular streaks, irregular dots or globules, lentigo malignas, and acral melanomas. A blue-white veil is easily identifiable by the blue-whitish veil that is evident flowing through the pigmented lesions’ pigment globular network. It presents with homogenously pigmented, black and brown lesions and is associated with thickening of the epidermis. Regression has aspects quite similar to the blue-white veil, in which blue and white sections can be seen throughout regions of the pigmented lesion. The white portions look like a scar, while the blue portions present as a gray-blue, peppered with dots throughout the lesion. A lentigo maligna is characterized by a rollicking and an increased number of atypical melanocytes at the dermal-epidermal junction and above it. The parallel ridge pattern showing prominent pigmentation on the ridges of the skin markings is a characteristic dermoscopic feature often detected in malignant melanoma and melanoma in-situ on acral skin. Also, an irregular, diffuse pigmentation is often detected in malignant melanoma on acral skin. Presence of any one of these features is enough to suspect a melanoma and gives good cause to biopsy.

To Biopsy or Not To Biopsy

In our approach it is not critical to separate lesions into melanocytic or non-melanocytic as long as a lesion which needs biopsy is biopsied. As shown above, if a lesion has a common, benign pattern, there is usually no need for a biopsy. However, if the pattern is unknown or has suspicious features, biopsy is warranted. Pattern analysis as an algorithm is similar to our approach and identifies certain features to diagnose a melanoma, yet it is different because it focuses on distinguishing benign lesions from malignant ones, whereas we simply look to whether we should biopsy or not.

Discussion

In our hands, this method has provided a unique tool for the assessment of pigmented lesions and is not tedious or time-consuming. This simplified method will encourage the use of dermoscopy as a diagnostic aid in the community, where time is a premium.

Other algorithms may not always be practical and are not used by many in North America. Dermatologists who are very well trained in these algorithms have high skin-cancer detection rates; however, dermatologists who do not have low detection rates of skin cancer. SPD can be a useful tool for beginners in dermatoscopy to identify lesions that need to be biopsied. Screening is important, however, we find it more important to err on the side of caution and biopsy any and all suspicious lesions. Many dermoscopic algorithms have been validated as useful tools in aiding sensitivity of melanoma detection, yet experience is the most important factor in determining how effective such a clinical tool can be. Just as a dermatopathologist is more apt to accurately diagnose a histological slide than a primary care physician, those dermatologists with experience using dermoscopy are more proficient at recognizing common dermoscopic patterns than novice dermatologists. Dermatologists alone have unique expertise in melanoma diagnosis and the clinical workup of melanoma through visual inspection and the use of analytic aids such as dermoscopy. With its easy learning curve, SPD is for those who understand patterns to learn the essentials of dermoscopy, and with this strong foundation, may build their knowledge of this valuable clinical tool.

Conclusion

In our hands, we have found Simple and Practical Dermoscopy to be the quickest, most effective way to assess the need for biopsy of a pigmented lesion. Due to the simplicity of the method, anyone can learn and incorporate it into even the busiest of practices. This gives clinicians another device for assessing pigmented lesions and diagnosing malignant melanoma earlier than ever before. It is our belief that this simple protocol will encourage the use of dermoscopy in the community and allow for better patient care.

References


<table>
<thead>
<tr>
<th>Pattern</th>
<th>Biopsy or Not?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patchy network</td>
<td>NO</td>
</tr>
<tr>
<td>Homogeneous brown or blue</td>
<td>NO</td>
</tr>
<tr>
<td>Starburst (commonly in Spitz/Reed nevi)</td>
<td>NO</td>
</tr>
<tr>
<td>Reticular</td>
<td>NO</td>
</tr>
<tr>
<td>Globular</td>
<td>NO</td>
</tr>
<tr>
<td>Reticulo-globular</td>
<td>NO</td>
</tr>
<tr>
<td>Milia-like cysts</td>
<td>NO</td>
</tr>
<tr>
<td>Comedo-like openings</td>
<td>NO</td>
</tr>
<tr>
<td>Moth-eaten border</td>
<td>NO</td>
</tr>
<tr>
<td>Honeycomb network</td>
<td>NO</td>
</tr>
<tr>
<td>Red-blue lacunas</td>
<td>NO</td>
</tr>
<tr>
<td>Red-blue to red-black diffuse homogeneous areas</td>
<td>NO</td>
</tr>
<tr>
<td>Central hypopigmented area with peripheral network</td>
<td>NO</td>
</tr>
<tr>
<td>Parallel furrow</td>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Biopsy or Not?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent pigment network</td>
<td>YES</td>
</tr>
<tr>
<td>Arborizing vessels</td>
<td>YES</td>
</tr>
<tr>
<td>Leaf-like areas</td>
<td>YES</td>
</tr>
<tr>
<td>Large blue-gray ovoid nests</td>
<td>YES</td>
</tr>
<tr>
<td>Multiple blue-gray globules</td>
<td>YES</td>
</tr>
<tr>
<td>Spoke wheel areas</td>
<td>YES</td>
</tr>
<tr>
<td>Blue-white veil</td>
<td>YES</td>
</tr>
<tr>
<td>Atypical pigment network</td>
<td>YES</td>
</tr>
<tr>
<td>Multiple colors (more than 5)</td>
<td>YES</td>
</tr>
<tr>
<td>Regression</td>
<td>YES</td>
</tr>
<tr>
<td>Irregular streaks and globules</td>
<td>YES</td>
</tr>
<tr>
<td>Parallel ridge</td>
<td>YES</td>
</tr>
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</table>
Table 3 - Melanocytic and Non-Melanocytic Pigmented Lesions

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanocytic Lesion</td>
<td>Network&lt;br&gt;Globules</td>
</tr>
<tr>
<td>Seborrheic Keratosis</td>
<td>Multiple milia-like cysts&lt;br&gt;Comedo-like openings&lt;br&gt;Fissures&lt;br&gt;Network-like structures&lt;br&gt;Fingerprint-like structures&lt;br&gt;Sharply demarcated and/or moth-eaten borders</td>
</tr>
<tr>
<td>Basal Cell Carcinoma</td>
<td>Absent pigment network and one of the following:&lt;br&gt;Arborizing vessels&lt;br&gt;Leaf-like areas&lt;br&gt;Large blue-gray ovoid nests&lt;br&gt;Multiple blue-gray globules&lt;br&gt;Spoke wheel areas</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Red-blue lacunas&lt;br&gt;Red-blue to red-black diffuse homogeneous areas</td>
</tr>
<tr>
<td>Dermatofibroma</td>
<td>Central hypopigmented area&lt;br&gt;Peripheral network</td>
</tr>
</tbody>
</table>

Figure 1: Network
Figure 2: Central Hypopigmentation
Figure 3: Blue-White Veil
Figure 4: Irregular Pigmentation
A 69-year-old male with a past medical history significant for pancreatic adenocarcinoma presented with a complaint of “rash” on the hands and arms. He had noticed bright red swelling on his forearms, hands, and chest over the previous two weeks. He denied any prior treatments for these areas. On physical exam, there were several 5-11mm, light brown, hyperkeratotic papules and plaques with halos of dusky erythema involving the bilateral dorsal hands, forearms, and anterior distal upper extremities (Figure 1). Similar lesions were noted on sun-exposed areas of the anterior chest (Figure 2).

**Diagnosis: Capecitabine Drug Reaction**

The patient had been treated with capecitabine, an oral chemotherapeutic agent currently FDA-approved for the treatment of metastatic colorectal and breast cancer as well as adjuvant therapy for stage III colon cancer. The active metabolite of capecitabine is 5-fluorouracil (5-FU). We present a case of a classic 5-FU-like cutaneous reaction from capecitabine in a 65-year-old male with pancreatic cancer.

**ABSTRACT**

Capecitabine is an oral chemotherapeutic agent currently FDA-approved for the treatment of metastatic colorectal and breast cancer, as well as adjuvant treatment for stage III colon cancer. The active metabolite of capecitabine is 5-fluorouracil (5-FU). We present a case of a classic 5-FU-like cutaneous reaction from capecitabine in a 65-year-old male with pancreatic cancer.

<table>
<thead>
<tr>
<th>Selected Differential Diagnosis of Forearm Eczema</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic Keratoses</td>
<td>Rough, red papules in sun-exposed skin</td>
</tr>
<tr>
<td>Phototoxic Drug Reaction</td>
<td>Blistering and erythematous reaction in sun-exposed skin</td>
</tr>
<tr>
<td>Allergic Contact Dermatitis</td>
<td>Intensely pruritic erythema and vesicles following allergen exposure</td>
</tr>
<tr>
<td>Chronic Irritant Dermatitis</td>
<td>Xerosis progressing to chapped, burning vesicles following chronic chemical exposure</td>
</tr>
<tr>
<td>Subacute Cutaneous Lupus Erythematosus</td>
<td>Annular or psoriasiform eruption on sun-exposed areas</td>
</tr>
</tbody>
</table>
A CASE REPORT: CUTANEOUS CRYPTOCOCCUS IN HIV/AIDS PATIENTS

Nick Zilieris, D.O., Stanley Skopit, D.O., FAOCD

ABSTRACT
Cryptococcus is an encapsulated yeast with more than 50 species. The species C. neoformans var. neoformans is a dimorphic fungus that causes infections mostly in the immunocompromised host. Cutaneous manifestations occur in 10-15% of patients with disseminated Cryptococcus infection. The lesions seen in AIDS patients are typically characterized as ‘molluscum-like’ umbilicated papules. The clinical presentation, pathogenesis, pathological findings, and treatment options will be reviewed.

Introduction
Cryptococcus is an encapsulated yeast with more than 50 species. The species C. neoformans var. neoformans is a dimorphic fungus that causes infections mostly in the immunocompromised host. Cutaneous manifestations occur in 10-15% of patients with disseminated Cryptococcus infection. The lesions seen in AIDS patients are typically characterized as ‘molluscum-like’ umbilicated papules. The clinical presentation, pathogenesis, pathological findings, and treatment options will be reviewed.

Case Description
A 53-year-old female, with no significant past medical history, presented to the emergency department with a one-month history of intermittent, bi-temporal headache that was described as pounding, radiating to her neck, and rating an 8/10 in severity. The headache was associated with photophobia, nausea, vomiting, fever, night sweats, and chills.

The patient had visited two other emergency rooms that discharged her only with NSAIDS. Upon further questioning, the patient admitted to a weight loss of 8 lbs within the past month. She denied blurry vision, hearing loss, chest pain, shortness of breath, abdominal pain, diarrhea, and seizures. Of particular note, the patient noticed raised lesions on her face, and “bruise-like” lesions on her left arm that started one month ago, coinciding with the onset of her headaches. The patient denied any allergies. The family history was non-contributory. She was not taking any medications.

The social history included: her living with her three sons, IV heroin use (last drink was two months prior), prior smoker of ten pack years, and husband dying three years earlier secondary to a complication from HIV/AIDS. She had had previous HIV tests, including three negative and one positive that were approximately three years prior, but no treatment was sought. The patient stated that she was in denial of the last positive test. On physical exam, the patient had one 2 mm x 2 mm and one 1 mm x 1 mm flesh-colored papule, both hard and smooth with a central umbilication, located on the right cheek and right philtrum (Figure 1). On her left arm, there were multiple erythematous macules of varying sizes, some with a healed central crust and surrounding telangiectasias (Figure 2).

The hospital course: She tested positive for HIV with CD4 57 and VL 22,000. Lumbar puncture revealed many encapsulated yeast consistent with Cryptococcal neoformans, two sets of blood cultures grew yeast, and the serum cryptococcal antigen level was greater than 1:10,000. The patient was empirically started on vancomycin 1 gm, ceftriaxone 2 gm, ampicillin 2 gm, and acyclovir 500 mg. For the fungal infection, the patient was started on liposomal amphotericin B 250 mg daily and flucytosine 500 mg every 6 hours. Additional testing revealed the patient to have hepatitis C, respiratory syncytial virus, decompensated diastolic heart failure, and severe thrombocytopenia. Within three days of hospitalization, she passed away from massive pulmonary hemorrhage and ventricular fibrillation arrest.

Discussion
Cryptococcus is an encapsulated yeast that contains more than 50 species. The two most common species are: C. neoformans var. neoformans and C. neoformans var. gattii. C. neoformans var. neoformans, a dimorphic fungus, is found worldwide, mainly around pigeon droppings, and mostly causes infections in immunocompromised hosts. C. neoformans has two serotypes that cause infection in humans, types A and D.4 The species C. neoformans var. gattii, which is found around eucalyptus trees in subtropical and tropical climates, causes 70-80% of infections in immunocompetent hosts.5 C. gattii also has two serotypes that infect humans, types B and C. Cryptococcus has become a major opportunistic infection in the immunocompromised host, with up to 90% of infections occurring in AIDS patients with CD4 <50. In the post-HAART era, the incidence has decreased but still can occur in 7-15% of these patients.6

The cryptococcal spores enter the body via the lungs. In the alveoli, the yeast comes into contact with alveolar macrophages, which elicit an inflammatory response. Pulmonary infection is often asymptomatic, but the organism may disseminate hematogenously to extrapulmonary tissues, including the brain, skin, bone, and less commonly the eye, prostate gland, and urinary tract depending on the immune status of the individual.7 The major virulence factors are the polysaccharide capsule, its ability to grow at 37 degrees, and phenol oxidase enzyme. While the exact mechanism of the polysaccharide capsule is not fully understood, it is clear that the modification of its outer envelope and capsule increases its ability to resist phagocytosis.8 The phenol oxidase enzyme is involved in the production of melanin, which makes the organism resistant to leukocyte attack, decreasing lymphocyte proliferation and tumor necrosis factor production.9

The central nervous system is the most common secondary site of infection because the cerebrospinal fluid lacks complements and immunoglobulins, making it an ideal site for growth of the yeast. Thus, cryptococcal meningitis is the most common presentation seen clinically in the immunocompromised host.10 Cutaneous manifestations are the second most common secondary site of infection after hematogenous dissemination, occurring in 10-15% of patients.11 Most commonly found on the head and neck, the lesions’ characteristics are various. The most common morphologic presentation is “molluscum-like,” umbilicated papules of varying sizes which may have a gelatinous quality with a hemorrhagic central crust.12 The lesions may be erythematous, edematous, warm, nodular, papulostular, vesicular, acniform, or ulcerative in nature. They can be isolated or occur as multiple lesions. Additionally, cutaneous lesions can either mimic Kaposi’s sarcoma or contain both Kaposi’s sarcoma and Cryptococcus organisms.13 14 15

Given that cutaneous disease is most likely disseminated, a complete workup for systemic involvement is paramount. This includes a thorough history and physical examination, chest radiography or CT scanning to evaluate
pulmonary involvement, and lumbar puncture. Diagnostic testing may include the latex agglutination test or enzyme-linked immunosorbent assay, which are both sensitive and specific for testing blood or cerebrospinal fluid. Direct preparations are performed on a drop of serum or exudate placed on a slide. The cells are large, 5-15 μm, seen as budding cells with capsules. The capsule can be visualized with periodic acid-Schiff, mucicarmine, or India ink staining. The cutaneous diagnosis can be confirmed by tissue culture of a skin biopsy specimen. The specimen colony should appear moist, shiny, and white on Sabouraud dextrose agar, but it may darken with aging. Results are usually positive. The specimen can be pigmented on Guizotia seed medium. Histologically, infiltrates have been described as consisting of two patterns. The first is the granulomatous type, showing sheets of histiocytes phagocytizing abundant budding yeast forms surrounded by clear halos. The second is the gelatinous type, where the fungi appear floating free in pools of mucin with little or no inflammation.

The choice of treatment for disease caused by Cryptococcus neoformans depends on both the anatomic sites of involvement and the host's immune status. For primary cutaneous disease, recommended treatment is oral azole therapy, fluconazole, for 36 months. Unfortunately, for disseminated disease in immunocompromised patients with meningitis, the treatment still results in 10-25% mortality. The preferred treatment algorithm begins with induction therapy of two drugs: amphotericin B 0.7-1 mg/kg/day (alternatively, liposomal amphotericin B can be used because it is associated with fewer adverse events), plus flucytosine 100 mg/kg/day for two weeks. This should be followed by monotherapy with fluconazole 400 mg/day (alternatively, itraconazole may be substituted) for a minimum of 10 weeks. After 10 weeks of therapy, the fluconazole dosage may be reduced to 200 mg/day, depending on the patient's clinical status. Even with adequate treatment, one-third of patients experience mycological or clinical failure. As a result, fluconazole should be continued for life. However, studies have shown that treatment can be discontinued under the following circumstances: completion of one year of treatment with an azole, current HAART treatment, a CD4 >100 for at least three months, and a nondetectable or low viral load.

Reference
When the flares of dermatitis strike... 
On target relief

KENALOG®
SPRAY
Triamcinolone Acetonide
Topical Aerosol USP

Precision application when treating hard to reach areas

- Indicated for relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses
- Systemic absorption of topical corticosteroids has produced reversible, hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing’s syndrome, hyperglycemia, and glucosuria in some patients. (See the Precautions section in Full Prescribing Information)
- Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushing’s syndrome than mature patients because of a larger skin surface area to body weight ratio.

The Nozzle Makes the Difference!

For topical use only
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RANBAXY
KENALOG® SPRAY
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Topical Aerosol, USP
For dermatologic use only
Not for ophthalmic use

Brief Summary: Please see full prescribing information for complete product information.

DESCRIPTION
Each gram of spray provides 0.147 mg triamcinolone acetonide in a vehicle of isopropyl palmitate, dehydrated alcohol (10.5%), and isostearate propellant.

INDICATIONS AND USAGE
Kenalog Spray (Triamcinolone Acetonide Topical Aerosol USP) is indicated for relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

CONTRAINDICATIONS
Topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS
General
Systemic absorption of topical corticosteroids has produced reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushings syndrome, hyperglycemia, and glucosuria in some patients.

Conditions which augment systemic absorption include the application of the more potent steroids, use over large areas, prolonged use, and the addition of occlusive dressings. Therefore, patients receiving a large dose of any potent topical steroid applied to a large surface area or under an occlusive dressing should be evaluated periodically for evidence of HPA axis suppression or of adrenocortical insufficiency (see Laboratory Tests). For this reason, a patient should not exceed the dose prescribed by the physician.

Recovery of HPA axis function and normal maintenance dosages are generally prompt and complete upon discontinuation of the drug. Infrequently, signs and symptoms of steroid withdrawal may occur, requiring supplemental systemic corticosteroids. Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary.

Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity (see PRECAUTIONS, Pediatric Use). If irritation develops, topical corticosteroids should be discontinued and appropriate therapy instituted.

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, the corticosteroid should be discontinued until the infection has been adequately controlled.

Information for the Patient
Patients using topical corticosteroids should receive the following information and instructions:

1. This medication is to be used as directed by the physician. It is for external use only; avoid contact with the eyes and inhalation of the spray.
2. Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
3. The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
4. Patients should report any signs of local adverse reactions especially under occlusive dressing.
5. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.

Laboratory Tests
A urinary free cortisol test and ACTH stimulation test may be helpful in evaluating HPA axis suppression.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential or the effect on fertility of topical corticosteroids.

Studies to determine mutagenicity with prodditions and hydrocortisone showed negative results.

Pregnancy: Teratogenic Effects
Category C. Corticosteroids are generally teratogenic in laboratory animals when administered systemically at relatively low dosage levels. The more potent corticosteroids have been shown to be teratogenic after dental application in laboratory animals. There are no adequate and well-controlled studies in pregnant women on teratogenic effects from topically applied corticosteroids. Therefore, topical corticosteroids 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
It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in breast milk. Systemically administered corticosteroids are transferred into breast milk in quantities not likely to have a deleterious effect on the infant. Nevertheless, caution should be exercised when topical corticosteroids are administered to a nursing woman.

Pediatric Use
Pediatric patients may demonstrate greater susceptibility to topical corticosteroid-induced HPA axis suppression and Cushings syndrome than adults because of a larger skin surface area to body weight ratio.

HPA axis suppression, Cushings syndrome, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include linear growth retardation, delayed weight gain, low plasma cortisol levels, and absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema.

Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.

ADVERSE REACTIONS
The topical local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and milia.

DOSEAGE AND ADMINISTRATION
Directions for use of the spray can are provided on the label. The preparation may be applied to any area of the body, but when it is sprayed about the face, care should be taken to see that the eyes are covered, and that inhalation of the spray is avoided.

Three or four applications daily of Kenalog Spray (Triamcinolone Acetonide Topical Aerosol) are generally adequate.

Occlusive Dressing Technique
Occlusive dressings may be used for the management of psoriasis or other recalcitrant conditions. Spray a small amount of preparation onto the lesion, cover with a pliable nonocclusive film, and seal the edges. If needed, additional moisture may be provided by covering the lesion with a dampened cloth or cotton, cloth before the nonocclusive film is applied or by briefly wetting the affected area with water immediately prior to applying the medication. The frequency of changing dressings is best determined on an individual basis. It may be convenient to apply the spray under an occlusive dressing in the evening and to remove the dressing in the morning (i.e., 12-hour occlusion). When utilizing the 12-hour occlusion regimen, additional spray should be applied, without occlusion, during the day. Reapplication is essential at each dressing change.

If an infection develops, the use of occlusive dressings should be discontinued and appropriate antimicrobial therapy instituted.

Store at room temperature; avoid excessive heat.

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November 2007

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IDENTICAL SKIN NODULES IN MULTIPLE FAMILY MEMBERS

David A. Kasper, DO, MBA,* Brian Kopitzki, DO,** Kimball Silvertown, DO***
* 2nd-year Dermatology Resident, Genesys Regional Medical Center, Grand Blanc, MI
** Dermatology Attending, Genesys Regional Medical Center, Grand Blanc, MI
*** Program Director, Genesys Regional Medical Center, Grand Blanc, MI

ABSTRACT
We present a case of a 20-year-old female who presented to our office with a history of multiple, occasionally tender lesions on her bilateral arms, chest, back, neck and jaw line. Her immediate family members had had similar lesions. She noted her paternal uncle recently underwent a total colectomy.

History
A 20-year-old female with a past medical history of asthma, depression and headaches presented to our office with a history of multiple, occasionally tender, skin-colored, firm papules on her bilateral arms, chest, back, neck and jaw line. She disclosed that some of her immediate family members have had similar lesions and noted her paternal uncle recently underwent a total colectomy.

Examination
The physical examination revealed multiple 5-9mm, skin-colored, firm, somewhat tender and mobile papules and subcutaneous nodules on the bilateral upper extremities, chest, back, neck and jaw line (Figures 1 and 2). No crusting, bleeding, drainage or other symptoms were present. No pigmented ocular fundus changes were identified on an undilated exam. No palpable thyroid nodules were appreciated.

Laboratory
The patient was referred to a genetic-testing center at a major university for work-up. The genetic testing revealed a specific alteration in the APC gene, called 5986-5939delACAA, identified on chromosome 5. The patient reported that this gene mutation has also been attributed to her immediate family members. Her complete blood count, thyroid function tests, ANA, electrolytes, renal and liver function tests were within normal limits.

Histopathology
An excision was performed of a lesion on the right neck. The biopsy results demonstrated a nodular proliferation of cornified matrical cells ("shadow cells") that are calcium laden. A patchy infiltrate comprised of histiocytes and lymphocytes is present in the surrounding dermis (Figure 3).

Diagnosis
Gardner syndrome

Discussion
Gardner syndrome, named after Eldon J. Gardner and identified in the 1950s, is an autosomal-dominant disorder associated with mutations in the adenomatosis polyposis coli (APC) gene located on chromosome 5q21.1 The APC gene is a tumor suppressor gene that regulates beta-catenin, a protein that controls cell growth. Mutations in this gene promote tumor formation. Approximately 20-30% of newly diagnosed cases are reported to have new mutations or arise from mosaic inheritance.2-4 The incidence of GS in the United States is 1 in 14,000. The prevalence between males and females remains fairly constant, with the disorder affecting both sexes equally.2,4 On average, GS is diagnosed at 22 years of age, although most colonic polyps have formed during puberty. Progression to malignancy is almost 100% in patients if no surgical intervention is performed, with death due to colonic carcinoma by the sixth decade.1,2 The malignant progression is observed in patients 30-50 years old.1,4

The most common extracolonic finding in GS is epidermoid cysts, which occur in 50-65% of patients.2,4 Of note, the epidermoid cysts in GS can be differentiated from ordinary cysts. The cysts in GS tend to be asymptomatic (although they may be pruritic and inflamed), occur in multiples, and form around pubertal for the head, neck, and extremities. Other cutaneous physical findings in GS include fibromas, lipomas, and pilomatrixomas. The non-cutaneous manifestations include desmoid tumors, osteomas, congenital hypertrophic retinal pigmented epithelium (CHRPE), gastrointestinal polyps and dental anomalies including odontomas and unerupted or supernumerary teeth. Neoplasms associated with GS include papillary thyroid carcinoma, desmoid tumors, hepatoblastoma, biliary and endocrine neoplasms, CNS tumors and periampullary adenomas.

Individuals afflicted with GS have an inevitable risk of developing malignant degeneration, with the GI polyps, affecting to colorectal carcinoma. Since these polyps have a 100% risk of undergoing malignant transformation, early diagnosis of GS is of utmost importance.1,4 The current surveillance recommendations include upper and lower endoscopies at least annually and fecal occult blood. Other surveillance screenings include thyroid screening by physical examination and ultrasonography, genetic studies and counseling of family members, specifically first-degree relatives. Since over half of GS patients have dental anomalies including odontomas, osteomas, and abnormal teeth, radiological examination of the head and mandible as well as the long bones is necessary. Other recommendations include alpha-fetoprotein levels and upper and lower abdominal ultrasonography to rule out hepatoblastomas and endocrine neoplasms, respectively.

On histopathology, most epidermoid cysts in GS are similar to non-GS cysts. However, in one study, 63% of cysts examined had one or more pilomatrixoma-like changes.4 These features included columns of shadow cells, basophilic matrical cells in the cyst lining, and calcification.

Generally, the cutaneous lesions in GS do not warrant treatment. However, depending on the lesions becoming symptomatic or posing a cosmetic concern, or on their location, treatment would involve surgical excision. Given the high rate (~100%) of malignant potential in the GI polyps, prompt diagnosis is critical for early intervention. Total colectomy is warranted to prevent colonic carcinoma, especially if there are greater than 30 lesions or biopsy results in dysplasia or malignant degeneration.1,4

Our patient underwent genetic studies and counseling. She has undergone annual esophagogastroduodenoscopies and colonoscopies. These annual surveillance studies identified tubular adenomas in the duodenum and fundal polyps with foveolar hyperplasia. Currently, she is being managed conservatively, although our patient understands the malignant potential and risks associated with GS. She is being evaluated by ophthalmology and radiology to rule out retinal changes and osteoma formation, respectively. Her primary care physician is monitoring for thyroid and endocrine abnormalities. Although there is no consensus on thyroid screening, suspicious lesions during routine examinations should have thyroid imaging studies performed.

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References

INTRAVENOUS PYOGENIC GRANULOMA

Scott Deckelbaum, DO,* Paul Shitabata, MD,** Mark Horowitz, DO,*** David Horowitz, DO, FAOCDS, FAAD****
*Second-year Dermatology Resident, Western University - Pacific Hospital, Long Beach, CA
**Director, Dermatopathology, Harbor-UCLA Dermatology and Western University; Medical Director, Dermatopathology Institute, Torrance, CA
***Dermatology Attending, Western University - Pacific Hospital, Long Beach, CA
****Dermatology Residency Program Director, Western University - Pacific Hospital, Long Beach, CA

ABSTRACT

Intravenous pyogenic granuloma is a rare form of the common mucocutaneous pyogenic granuloma.

Case Report

A 32 y/o male with an unremarkable medical history presented with a subcutaneous mass on his forehead. It arose spontaneously approximately three months prior to his visit. It was rather abrupt in onset, enlarging over several days, and then remained stable. There was no discomfort associated with the mass unless the patient was wearing his hard hat at work. He sought treatment because the mass became tender throughout his work day as his helmet created pressure. It was localized to his forehead, just under the head band of his helmet. He denied any previous trauma or abnormal pressure to the area other than the uniform pressure applied by the head band in his helmet.

On physical exam, there was a small, 6 mm, nondescript, palpable subcutaneous mass in the upper lateral aspect of his left forehead. There were no overlying signs of erythema, discoloration, or disruption of the normal skin barrier.

Initial diagnosis was presumptively an epidermal cyst. Given the above symptoms, our patient elected for surgical removal. An elliptical excision through the subcutaneous fat was performed with complete excision of the lesion. Hemostasis was achieved with electrocautery and suture ligation. Three months post operatively, there has been no recurrence. Histopathology revealed a proliferation of capillary-sized vessels predominantly within a larger vessel, favoring a diagnosis of intravenous pyogenic granuloma (IVPG).

Discussion

Pyogenic granulomas are benign vascular lesions that usually occur on cutaneous or mucosal surfaces. We report a case of the much less common intravenous pyogenic granuloma (also reported as intravascular pyogenic granuloma in the literature). Cooper et al. presented, in 1979, a study of 18 cases of intravenous pyogenic granuloma occurring in the head and neck.1 Since that initial report, intravenous pyogenic granulomas have been reported arising in numerous clinical settings. We have found a case similar to our patient of an IVPG occurring in a soldier that “made it difficult” for him to wear his helmet.2 Several cases of IVPG are reported arising in the hand.3,4,5 Ulbright et al. reported an IVPG arising in the external jugular vein of a 12-year-old boy.3 Pradhan et al. reported an IVPG arising in the iliac vein of a 75-year-old woman.4 In 1985, Archives of Ophthalmology published a report of two cases of IVPG involving the ocular adnexa.5 At least one case of an IVPG arising within an arteriovenous malformation is reported.6

As with our case, many of the IVPG found were diagnosed either intra-operatively or post-operatively. As deep tumors, they often present as a nonspecific mass with a clinical differential that may depend on the location. In his review of cases, Cooper et al. suggested that the discovery of an intravenous nodule should prompt the inclusion of IVPG into the differential.7

However, histologic evaluation remains the primary means of diagnosis following surgical excision. As demonstrated in Figures 1-3, our histologic findings were of a partially circumscribed proliferation of capillary-sized vessels predominantly localized within a larger vessel. Qian et al. published a brief review of the immunohistochemical findings of IVPG.8 Our immunohistochemical profile showed similar findings, with endothelial cells positive for CD31, suggesting a vascular proliferation. The larger surrounding vessel staining was positive for smooth muscle actin and elastin, confirming its vascular integrity. A Ki-67 did not show significant proliferation. The histopathologic findings will distinguish this intravascular tumor from others including inflammatory angiomatosus nodules, intravascular papillary endothelial hyperplasia and angiosarcomas.9

While IVPG is a rare etiology for subcutaneous nodules, it should be included in the differential diagnosis for dermatologists performing surgery of the skin. Complete surgical resection, as with mucocutaneous pyogenic granulomas, should be curative. If identified intra-operatively, segmental excision of the involved vessel should be accomplished to avoid recurrence.4

References

Apocrine Carcinoma of the Skin Overlying the Temple: A Case Report and Review of the Literature

Theresa A. Zaleski, MSIV,* Amin Maghari, MD,** W. Clark Lambert, MD, PhD***
*Fourth-year Osteopathic Medical Student, University of Medicine and Dentistry of New Jersey - School of Osteopathic Medicine, Stratford, NJ
**Dermatopathology Fellow, University of Medicine and Dentistry of New Jersey – New Jersey Medical School, Newark, NJ
***Dermatopathology Director, University of Medicine and Dentistry of New Jersey - New Jersey Medical School, Newark, NJ

ABSTRACT

Apocrine adenocarcinoma is a rare entity most commonly found in middle-aged to elderly patients in locations such as the axillae, where apocrine glands are naturally found in highest distribution. We report the unique occurrence of an apocrine adenocarcinoma of the temple in a 27-year-old female. Clinically, the lesion appeared cystic with drainage of clear fluid. Given its location, this apocrine carcinoma may have arisen either from modified apocrine glands of the eyelid, known as Moll’s glands, or from an ectopic or exaggerated distribution of apocrine glands beyond that of those generally accepted to be anatomic in nature.

Introduction

Apocrine carcinoma is a rare malignant tumor derived from apocrine glands most commonly located in the axillae or eyelid. Tumors of this subtype have previously been described in patients ages 18 to 81 years old. Clinically, apocrine carcinoma presents as a firm nodule or plaque ranging from 0.2 to 2 centimeters in size.7 Apocrine carcinoma is classically considered to be an aggressive tumor with the propensity to first metastasize to regional lymph nodes and potentially cause death secondary to visceral metastases.7 The treatment of choice for this malignant neoplasm is wide surgical excision. Some cases of patients treated with adjuvant radiotherapy in advanced disease have been reported, with chemotherapy typically reserved for those cases that cannot be treated surgically.7

Case Report

A 27-year-old female presented to the dermatology clinic complaining of a left temporal cyst, just lateral to her eye, which had been present for about a year. She reported occasional clear fluid draining from the mass but denied any increase in size and pain or redness. The patient had not experienced fevers at home and denied prior treatment of the cystic lesion. On clinical examination, the cystic lesion was measured to be 0.6 x 0.5 x 0.4 centimeters. At that time, surgical excision was performed.

The pathology from the surgical excision of the lesion is shown in Figures 1 through 6. The final pathologic diagnosis was determined to be papillary low-grade apocrine adenocarcinoma involving the dermis. The immunohistochemical stains showed that the tumor cells were immunoreactive for CEA, EMA, S-100 protein and GCDFP-15, which supported the diagnosis. The tumor was also found to have cystic components that are not typically characteristic of apocrine carcinomas. Of note, this case was reviewed by a second party in order to confirm the diagnosis in light of the fact that acinic cell carcinoma of the salivary glands (in our case, parotid gland) can sometimes show a papillary variant similar to the findings in this case.

Thus, it was necessary to rule out the possibility that this tumor was an extension from a deeper tumor of the parotid which is usually negative for GCDFP-15. It was not considered to be such and simply raised the possibility because of a similarity to acinic cell tumors.

Given the diagnosis of apocrine adenocarcinoma, the patient returned to the clinic for re-excision of the margins. Re-excision of the site was performed and extended to involve the outer corner of the left eyelid. A hypertrophic scar consistent with previous biopsy site changes with no evidence of tumor was reported.

Discussion

Apocrine adenocarcinoma is a rare, aggressive neoplasm found most commonly in older individuals, with no predilection for sex or race.1,4 This type of tumor can occur as multiple or single nodules or plaques most commonly located in the axilla, scalp, eyelid, anogenital region, or chest, where apocrine glands are naturally found to be in highest distribution.1,4 Occasional cases have been reported in various other locations, but to this date, no cases of an apocrine adenocarcinoma tumor of the skin overlying the temple region has been documented, with the exception of a case demonstrating a mucinous carcinoma of the skin with apocrine-like differentiation in a 70-year-old male.7 The etiology of apocrine carcinoma is largely unknown, but in some instances lesions have been known to arise from apocrine hamartomas, nevus sebaceous, or extra-mammary Paget disease.1 The prognosis associated with this neoplasm ranges from non-fatal courses with local invasiveness to death secondary to widespread metastases.3 The recommended treatment of apocrine adenocarcinoma is excision with wide margins and frequent follow-up, as this neoplasm is known for a high rate of recurrence.

Histopathologically, this tumor is described as a non-encapsulated lesion located in the lower dermis and subcutaneous tissue.2 Typically, tumor cells show variable pleomorphism, abundant eosinophilic cytoplasm, and decapitation secretion; however, the latter may not be present in all cases.2 Immunostains for GCDFP-15, an apocrine selective protein, generally are positive.8 Under the microscope, the specimen from this case showed a predominantly cystic neoplasm. The tumor cells have distinct cell margins, acidophilic cytoplasm with eosinophilic granules, and central vesicular nuclei with prominent nucleoli, on occasion showing decapitation secretions (Figures 3-5). The latter features described are consistent with previous cases of apocrine carcinoma found in literature. However, to our knowledge, this is the first apocrine carcinoma that demonstrates a primarily cystic neoplasm both under the microscope and on physical exam.

This case of apocrine carcinoma is unique in many aspects. It is uncommon for an apocrine adenocarcinoma to appear at such a young age. In general, it is believed that 61 years old is the median age at which apocrine carcinoma is found.7 As stated above, apocrine carcinomas are most commonly diagnosed in elderly and middle-aged patients. The location of the tumor is also of interest, as the temporal region is not known to have a high concentration of apocrine glands. Previous cases of apocrine adenocarcinoma of skin overlying the eyelid have been reported, but this neoplasm is believed to arise from Moll’s glands.7 The location of the tumor was not contiguous with the eyelid, but additional apocrine glands were found to be adjacent to the apocrine adenocarcinoma under the microscope (Figure 6). This finding raises the possibility that this could be a case of apocrine adenocarcinoma of Moll’s glands, although it is uncommon for these glands to be located beyond the lateral edge of eyebrow. There has been one case of apocrine carcinoma involving the forehead that has been previously described; however, this neoplasm occurred in a much older patient and described atypical histopathologic features in comparison with previously described apocrine carcinomas.8 Finally, it is unusual for apocrine adenocarcinoma of the skin to clinically present as a draining cystic lesion. The most common clinical presentation for this type of neoplasm is a solid nodule. Thus, it is imperative for the astute clinician to maintain a high index of
suspicion and a low threshold for removal of lesions that appear suspicious or do not have a clear benign dermatologic diagnosis. Once suspected, it is also important to make the distinction between metastatic adenocarcinomas and benign apocrine tumors as well as acinic cell tumors on pathology, as this would greatly change prognosis and management.

References
Cutaneous metastatic Crohn’s disease (CMCD) is a rare skin manifestation of inflammatory bowel disease. These lesions are located at sites remote from the gastrointestinal tract and therefore commonly misdiagnosed. There are relatively few cases reported in the literature. We describe a case of CMCD of the lower extremity of a middle-aged female without concurrent active Crohn’s disease (CD).

Case Report

A 49-year-old Caucasian female presented with a 10 cm x 12 cm lesion on her right lower extremity which has been progressively enlarging over the course of 2 months and is associated with an intermittent “stinging” sensation. The patient reported a history of smaller, self-healing, similar appearing lesions since her diagnosis of CD at the age of 22. She denied any recent flare of her gastrointestinal symptoms. The patient’s past surgical history was significant for 2 large bowel resections and 1 small bowel resection secondary to the inflammatory bowel disease. Her medications include 6-mercaptopurine 120 mg daily. Physical examination of her right posterior calf revealed tender, large, scattered, purulent ulcerations with underlying erythema (Figure 1). A 4 mm punch biopsy was performed of the right posterior calf. Special stains for acid-fast bacilli and fungi were performed (Figure 2).

Microscopic findings

Biopsy revealed ulceration accompanied by reactive hyperplasia of the epidermis and nonsuppurative granulomatous dermal inflammation. Multinucleated foreign body-type giant cells were present. Special stains for acid-fast bacilli and fungi were negative.

Discussion

Based on clinical history and histopathology, our diagnosis is CMCD. Crohn’s disease (CD) is a chronic inflammatory bowel disease with a relapsing course first described by Crohn et al in 1932. Extraintestinal manifestations of CD are common and can include cutaneous, arthritic, ocular, and pulmonary involvement. Cutaneous manifestations of CD are seen in 2-34% of cases, depending on whether perianal disease is considered a ‘cutaneous’ manifestation. Cutaneous lesions vary from reactive process such as pyoderma gangrenosum, to mucocutaneous extensions in the oral mucosa or perianal area, to nutritional deficiency syndromes secondary to malabsorption. However, one of the most intriguing cutaneous manifestations of CD is CMCD, a rare manifestation involving lesions that are histologically identical to those found in the bowel, specifically non-caseating granulomatous inflammatory lesions, at non-contiguous sites from the alimentary tract. This rare dermatological manifestation was first described in 1965 by Parks et al. Interestingly, the appearance of CMCD is not related to the severity of CD nor is it correlated with inflammatory bowel flares. In adult patients, CMCD arises most often after the onset of GI symptoms but may precede the onset of CD, complicating the diagnosis. In the pediatric population, CMCD precedes or coincides with the initial diagnosis of CD 50% of the time.

Cutaneous manifestations of CD can be divided into three categories: nongranulomatous or reactive, secondary to nutritional deficiencies, and granulomatous (Table 1). First, the non-granulomatous or reactive cutaneous lesions are the most common manifestations associated with CD and consist of a vast, heterogeneous group of dermatologic conditions such as pyoderma gangrenosum, erythema nodosum, Sweet’s syndrome and epidermolysis bullosa acquisita. Next, nutritional deficiencies related to malabsorption and destructive inflammation of CD can result in such conditions such as acrodermatitis enteropathica secondary to zinc deficiency, perleche secondary to iron deficiency, and purpura secondary to vitamin C and K deficiency.

The granulomatous group of extra-intestinal manifestations of CD is histologically similar to that of inflammatory bowel disease and can be further subdivided into two distinct categories. The first group consists of those lesions which are direct extensions of the inflammatory bowel disease occurring perianally or around stoma sites. Rarely, CD consists of non-caseating granulomatous skin lesions that are located at sites distant from the gastrointestinal tract. These lesions occur most commonly on extremities, flexural areas, or postauricular, but can occur anywhere as long as they are not contiguous with the alimentary tract. Many of the patients are women and the disease tends to occur in patients between the ages of 20-40 years. Clinically, cutaneous lesions may consist of small erythematous papules, which may enlarge and become nодular, then ultimately ulcerate. In the pediatric population, groin lesions are common manifestations of CMCD and genital lesions include testicular swelling and/or induration with or without erythema. Metastatic is somewhat of a misnomer as these lesions are not spreading hematogenously as in the oncological sense, but contain the same histopathology that characterizes CD.

The etiology of CMCD is unknown but postulated to be related to an exaggerated Th1 cell mediated response. Th1 responses produce INF-γ, a potent chemotactic mediator and activator for histiocytes. Some have hypothesized a bacterial id type of reaction. Crowson et al introduced the idea of “bacterial id,” that strongly suggests that intracellular bacteria are directly associated with the pathogenesis of intestinal CD, but not necessarily related to skin manifestations as evident by the lack of bacterial 16S rRNA in the corresponding skin biopsies. Another theory is autoimmune phenomenon, involving cross reacting antibodies between the gut and skin-based antigens. Recent research discovered similarities in tropomyosin isoforms of the gut, skin, eye, and joints that may contribute to autoimmunity.

CMCD does not have a typical clinical appearance and has been known as the ‘great imitator’ of cutaneous lesions. However, the location of lesions will help direct the formation of the differential diagnosis. For example, in patients with perineal lesions, sexually transmitted diseases such as lymphogranuloma venereum and syphilis must be included in the differential. For lesions located elsewhere, on the extremities and trunk, lesions may mimic infectious processes such as erysipelas or cellulitis. Histologically, the differential is expanded to include infectious, such as fungal and parasitic infestations, but also non-infectious granulomatous diseases, such as sarcoidosis, and foreign body reactions. Therefore, because the differential is so vast, a good history and physical exam is imperative to making the correct diagnosis.

Diagnostic studies should include a cutaneous biopsy with special stains, including Ziehl-Nielsen, periodic acid Schiff, methenamine silver, and polarizing light. The most characteristic pattern of CMCD is non-caseating granulomas with multinucleated giant cells surrounded by a rim of lymphocytes and plasma.
cells. A combination of a lichenoid and granulomatous dermatitis has been described in some cases.21

Treatment options consist of systemic and topical steroids, antibiotics, and immunosuppressive agents such as azathioprine, sulfasalazine, and methotrexate.22 One of the most effective treatments reported in the literature for cutaneous disease is oral metronidazole.23

Repeated curettage of ulcers can be effective as can wide excision, however recurrence is common.24 Colectomy of affected bowel is not an effective treatment for cutaneous lesions. Infliximab alone or in combination with methotrexate has been used in case reports with increased success rates and greater rates of remission of both the CMCD and CD.25,26

CMCD is a rare manifestation of CD. A clinical history of intestinal CD is a critical diagnostic clue as the differential diagnosis can be quite vast. Although our patient presented with quiescent CD status post large and small bowel resection, the clinicopathologic correlation was imperative in making the final diagnosis.

Table 1: Classification of cutaneous metastatic Crohn’s disease (CMCD) and examples.9-14

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<td><strong>Reactive (non-granulomatous)</strong></td>
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<td>- Pyoderma gangrenosum</td>
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<td>- Erythema Nodosum</td>
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<td>- Erythema subacute</td>
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<td>- Epidermolysis bullosa aguta</td>
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<td><strong>Nutritional</strong></td>
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<td>- Acrodermatitis enteropathica - zinc deficiency</td>
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<td>- Purpura - iron deficiency</td>
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<td><strong>Granulomatous</strong></td>
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<td>- Cutaneous metastatic Crohn’s Disease</td>
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References

Figure 1: Right posterior calf with tender, large, scattered, purulent ulcerations with underlying erythema

Figure 2: Punch biopsy of posterior calf revealed reactive hyperplasia of the epidermis and non suppurrative granulomatous dermal inflammation
ECCRINE POROCARCINOMA: A CASE STUDY AND REVIEW OF THE LITERATURE

D. Ryan Skinner, MSIV,* Julio Hernandez, MD, FAAD**
*Arizona College of Osteopathic Medicine, Glendale, AZ
**Board-certified Dermatologist, All One Skin Cancer, Glendale, AZ

ABSTRACT

Eccrine porocarcinoma is a rare tumor of the sweat glands that has shown both high recurrence rates and high rates of metastasis. Clinically, these tumors can present with a variety of clinical characteristics, the most common being a dome-shaped, reddish nodule. Although these tumors are found most commonly on the lower extremities, cases have been reported on the head, neck, upper extremities, and trunk. We present the case of an 81-year-old male with an eccrine porocarcinoma on his left inguinal area.

Introduction

An 81-year-old male presented to the clinic with a primary complaint of a painful nodule on his left inguinal region. The nodule appeared rapidly over a period of three to six weeks. He stated that the nodule was painful and that it occasionally wept fluid and bled. The patient is well known to the clinic, with a past medical history significant for multiple SCCs. The origin of an eccrine porocarcinoma is thought to be by one of two mechanisms. A tumor may arise from a malignant transformation of an already existing eccrine poroma, or it can arise de novo.5,6,12 Signs of this transformation are thought to include ulceration, spontaneous bleeding or a sudden growth phase that occurs from weeks to months.4,12 As this tumor arises from the intraepidermal portion of the eccrine duct (acrosyringium), it may invade the papillary dermis and the dermal lymphatics. Once it has invaded the dermal lymphatics, it may travel, reinvade the epidermis, and eventually give rise to multiple cutaneous metastases.10

Clinical features include a variety of presentations. Some of these include verrucous nodules, cauliflower-like infiltrative plaque, polyploidy growth that is ulcerated and bleeding, firm asymptomatic nodules that can be erythematous, violaceous or brown in color.2,5,8,10,13,14 According to one study, the most common clinical appearance is a dome-shaped, reddish nodule.8 Diameter can range anywhere from 1 to 10 cm, with averages in the 2 to 4 cm range.2,5,8,14 Dermatoscopy may be of little value in obtaining an accurate pre-surgical diagnosis; however, an atypical vascular pattern suggesting neovascularization within the lesion may be seen, thus prompting further investigation.9,15 In one study of 69 cases, the pre-surgical diagnosis was never correct. The lesions were most commonly believed to be SCC, SCC in situ or pyogenic granuloma.7

Histopathologically, look for nests of neoplastic cells invading the dermis, mature duct formation, intracrystalplasmic lumina, comedo-necrosis, intracrystalplasmic vacuoles, clear cell change, lymphovascular invasion, mitosis and presence of benign components (Figures 2 and 3). Diagnosis can be rendered on either an invasive architectural pattern and/or cytologic pleomorphism in a tumor showing eccrine differentiation.7,8 Histologically, differential diagnosis includes SCC, Paget’s, superficial spreading malignant melanoma and metastatic carcinoma.15 Staining for carcinoembryonic antigen is positive and S-100 protein negative for cells that line the neoplastic clefts and ducts.11

The relatively small number of cases of eccrine porocarcinoma have made it difficult to create a true standard of care.13 Wide local excision has been the most commonly used method of treatment but has been shown to lead to a recurrence rate of 20%.4,5 Mohs micrographic surgery has become increasingly popular in the treatment of eccrine porocarcinoma. One study showed no recurrences at up five years post Mohs excision.15

Patients with metastatic disease have traditionally fared poorly, with mortality rates up to 67%.7 Metastatic disease from eccrine porocarcinoma has in most cases responded poorly to chemotherapy or radiation.17 Various degrees of success have been achieved using cisplatin, flurouracil, tegafur-uracil, cyclophosphamide, bleomycin, vincristine, prednisone and methotrexate.10,14 One case of metastatic eccrine porocarcinoma showed complete remission using combined therapy of cisplatin, 5-flourouracil, radiation and irradiation therapy.18 Whole-body 18F-fluorodeoxyglucose positron emission tomography (FDG PET) has been used to detect recurrent lesions and lymph node invasion, as well as distant organ metastasis. In cases where distant metastases are suspected, FDG PET may be a useful diagnostic tool.19

Conclusion

Eccrine porocarcinoma is a malignant tumor of the eccrine sweat glands with high propensity to metastasize. Wide local excision has been the most common treatment, with recurrence as high as 20%. Recently, Mohs micrographic surgery has been more commonly used for the treatment of these lesions. Although more data should be gathered, based on our experience and numerous other successful case studies, we recommend Mohs micrographic surgery, along with close follow-up, as a primary treatment option for an eccrine porocarcinoma.

References


36 ECCRINE POROCARCINOMA: A CASE STUDY AND REVIEW OF THE LITERATURE
HYPERPIGMENTATION AFTER INFUSION WITH IRON FOR ANEMIA OF CHRONIC DISEASE

* Atlantic Dermatology Associates, P.A., Wilmington, NC
** University of North Carolina at Wilmington, Wilmington, NC
*** New Hanover Regional Medical Center, Wilmington, NC
**** Southeastern Nephrology, Wilmington, NC

ABSTRACT

Anemia of chronic disease often requires iron supplementation. Oral supplements are usually the first line of treatment because of cost, convenience, and safety. The GI tract has a limited capacity for iron absorption, so IM or IV substitution may be considered. Problems with IM injections include discoloration at the injection site as well as reports of sarcoma at the site of injection. Because of these dangers, many facilities will no longer do IM injections. Parenteral iron is now almost exclusively given by IV infusions. Patients with end-stage renal disease and chronic kidney disease are some of the patients that most frequently get parenteral iron. Side effects of IV infusion include anaphylaxis and tissue iron deposition, amongst other problems. We are reporting a case of a patient who had tissue iron deposition in her skin secondary to an IV infusion.

Case Report

This 29-year-old white female presented stating that she had an iron infusion in her right arm eight months prior. She was given this infusion of a newer large-dose iron because of iron deficiency seen with anemia of chronic disease while receiving erythropoietin-stimulating therapy epoetin alfa (Procrit). She developed end-stage renal disease as a result of Goodpasture’s syndrome. Her current renal transplant is rejecting and requires Procrit for anemia management. She stated that when she was having this infusion her vein “blew,” and she ended up having iron underneath the skin. She stated that over the prior eight months it had lightened up about 50%. She wanted to know what could be done about this and how it could be resolved faster.

Discussion

Hyperpigmentation from IV infusion of iron is a known complication. Even when watching patients closely, it can occur. To avoid injection leakage into the subcutaneous tissue, a Z track technique of injecting has been suggested in the past. This technique involves displacement of the skin laterally prior to the injection. When iron is deposited subcutaneously, it is difficult to reach this deep-seated iron with lasers or any other topical method. Lasers have been tried and have not resulted in complete clearance.

Cutaneous deposition of iron has been documented in the past, including secondary to Monsel solution. It has been reported that some homeopathic stores sell over-the-counter IM injections. If more people continue using self-administered iron injections, then we may see more problems of iron tattooing. There are currently four parenteral iron preparations approved in the United States; a fifth preparation, ferric carboxymaltose, is undergoing clinical trials.

1. Iron dextran (INFeD) has local and systemic reactions at 3.5 events per million doses.
2. Ferric gluconate complex (Ferrlecit) has reduced incidence of reactions, with 0.9 events per million doses per year.
3. Iron sucrose (Venofer) appears safer, even among those with prior history of iron dextran reaction, at 0.6 events per million doses.
4. Ferumoxytol (Feraheme), FDA-approved, is a semi-synthetic carbohydrate-coated superparamagnetic iron oxide that can be given as a rapid large dose of 510 mg (infusion rate: up to 30mg/second).
5. Ferric carboxymaltose (Ferinject) is a novel, stable iron complex given at a single dose of 1000 mg over 15 minutes. This is available in Europe, and clinical trials in the U.S. are currently underway.

It is yet to be determined if more local reactions will occur using these rapid infusions or large single-dose iron.

Treatment

The primary treatment for hyperpigmentation resulting from iron deposition is time. In this particular patient, we decided to add Umecta PD for her to use bid. Umecta was chosen secondary to its keratolytic and keratolytic properties. Urea gentles the intercellular matrix, which results in shedding of the most superficial layer of the skin and thereby increased cellular turnover. We are hopeful that this will result in decreased pigmentation. Umecta PD is a 40-percent urea cream, which is fairly safe to use. Side effects to be wary of include local skin irritation and, very rarely, anaphylaxis. This is a category C drug when administered to pregnant patients or those who desire to become pregnant. We have not promised her much as far as improvement, other than allowing time to assist with resolution. If the patient fails with Umecta PD and time, we will proceed with the Nd:YAG Q-switch laser; however, as mentioned previously, we are unsure of how much resolution this will bring, as the discoloration is located deep in the subcutaneous tissue. Watchful waiting will, however, be the main treatment of choice.

Conclusion

Iron tattoos have occurred in many patients through the years from both topical and parenteral iron administration. It appears time is a major factor in the resolution of deep parenteral depositions. We are very pleased with the fact that she has had 50% improvement in eight months, and we expect this resolution to continue.

References


Iron pigmentation on right antecubital fossa
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Case Report

A 49-year-old Asian male presented to the dermatology clinic with a clear mass on his chin for the past two years. The mass had been enlarging over the past few months. He stated that the mass was asymptomatic with no other physical complaints. He denied any past medical history or use of any medications. His review of systems was negative for weight loss, fever, night sweats and other constitutional symptoms. The physical exam revealed a 3.0 cm x 2.0 cm, clear, flesh-colored cystic structure on the chin with no tenderness on palpation. The lesion was removed using an elliptical excision, during which a profuse amount of mucin was drained.

The histology revealed expansive lakes of mucin diffusely replacing the dermis and focally extending into the skeletal muscle and biopsy margins. Within the lakes of mucin were islands of epithelial cells arranged in cohesive nests, forming ductal structures and focal cribriform features. These cells showed areas of possible apocrine differentiation with snouting, as well as mild variations in sizes and shapes. The shapes included round to oval nuclei. Focal peripheral palisading was also noted. There was no definitive attachment for the overlying epidermis. The mucin extended overlying epidermis. The mucin extended to oncology surgery to exclude visceral malignancy and for further treatment of his cancer.

Discussion

Primary mucinous carcinoma of the skin (PMCS) is a rare malignant neoplasm derived from sweat glands or their germinal structures.\textsuperscript{1,6} It was first described by Lennox et al. in 1952 and was revisited by Mendoza et al. in 1971, with only 228 cases reported in the literature since.\textsuperscript{7} Due to its rarity, metastasis from primary internal malignancies such as breast, gastrointestinal tract, lung, kidney, ovary, pancreas and prostate must be ruled out.\textsuperscript{1-15} PMCS’s origin is thought to favor eccrine more than apocrine differentiation.\textsuperscript{14} Some literature suggests that PMCS develops as a progression of abnormal apocrine or eccrine ducts, similar to mucinous carcinoma of the breast, ranging from ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ or a combination of the three. Also, it has been hypothesized that the presence of copious amounts of mucin serves as a physical barrier, compressing the tumor stroma and decreasing the rate of angiogenesis by inhibiting DNA synthesis, thus contributing to the benign nature of this tumor and its low metastasis potential.\textsuperscript{14,18} Differentiating between primary and metastatic mucinous carcinoma can be difficult. Levy et al. (2010) described 2/5 (40%) of PMCS stained positive for p63, while 3/5 (60%) of primary mucinous breast carcinomas also stained positive for p63.\textsuperscript{1} Some studies show no labeling of p63 in PMCS.\textsuperscript{2} Similarly, 20% of PMCS stains positive for CK 5/6.\textsuperscript{9} CK7 is positive in both PMCS and metastatic mucinous carcinoma of the breast, excluding primary colonic carcinomas.\textsuperscript{5,10} PMCS stains negative for CK 20, which is a marker for colonic mucinous carcinoma.\textsuperscript{1,4} Additionally, the location of the tumor can provide some assistance in differentiating between primary and metastatic. Metastatic tumors of the breast tend to show a preference for the chest, breast and axilla. The combination of the patient’s immunohistochemical stains and morphology of the tumor cells helps differentiate between PMCS and metastatic mucinous carcinoma. Our patient had a strong cytokeratin 7 and D2-40 reactivity, which favors the diagnosis of PMCS. In addition, the immunohistochemical stain was negative for cytokeratin 20, which also favors PMCS vs. colonic carcinoma. It was also less likely to be a metastasis from breast cancer because mucinous carcinoma of the breast rarely metastasizes to the skin.\textsuperscript{1,4}

Treatment of PMCS is wide local excision, with surgical margins of at least 1 cm

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and dissection of regional lymph nodes.\textsuperscript{1,3,7} In high-grade tumors, prophylactic lymph node dissection is recommended.\textsuperscript{12} There are several reports of successful treatment with Mohs micrographic surgery using low-molecular-weight immunostaining. However, according to Martinez et al. (2005), Mohs surgery can only be successful if there is no hematologic or lymphatic spread, thus favoring wide local excision over Mohs.\textsuperscript{6} Moreover, PMCS is not responsive to chemotherapy or radiation.\textsuperscript{1,6}

While PMCS has a favorable prognosis with a low mortality rate, patients should be counseled regarding the importance of annual follow-ups due to the high recurrence rate of 29.4\% and metastasis potential to the regional lymph nodes.\textsuperscript{6} It is crucial for dermatologists and dermatopathologists to be aware of primary mucinous carcinoma of the skin in order to diagnose it early and maintain consistent follow-up.

References

42 PRIMARY MUCINOUS CARCINOMA OF THE SKIN: A CASE REPORT AND REVIEW OF THE LITERATURE
TREATMENT OF LICHEN STRIATUS WITH HOMEOPATHIC CALCIUM CARBONATE

Robert J. Signore, DO, FAOCDF*  
*Dermatology Private Practice, Tinley Park, IL

ABSTRACT
Lichen striatus is a linear, unilateral inflammatory eruption of acute onset and unknown etiology. Lichen striatus occurs mainly in children, but it may also affect adults. Spontaneous involution can be expected in three to twelve months. However, some cases of lichen striatus may persist over a year. There is no consistently effective therapy for lichen striatus. Therefore, a safe, effective, and inexpensive treatment would be helpful to the clinical dermatologist. A case of lichen striatus in an infant is reported which rapidly resolved with oral homeopathic calcium carbonate.

Background
Lichen striatus is a self-limited, inflammatory linear eruption of sudden onset and unknown etiology. It is unilateral and usually appears on the arm, leg, or lateral neck. However, it can appear on any area of the body. Lichen striatus occurs mainly in children, but it may also affect adults. The eruption of lichen striatus consists of erythematous lichenoid papules which rapidly coalesce to form an irregular linear plaque. Histopathological features of lichen striatus include intercellular edema, with variable spongiosis and acanthosis. Focal liquefactive degeneration of the basal layer is present. A dermal perivascular infiltrate consisting of lymphocytes and histiocytes is present, which can be quite dense and can extend deeply. Spontaneous involution can be expected within three to 12 months. However, some cases can persist for more than a year. Clinical resolution can be followed by post-inflammatory hypopigmentation.1,2

Case Report
A healthy, 23-month-old female toddler was seen in our office with an asymptomatic, unilateral eruption on the right posterior thigh and lower leg of one week’s duration (Figure 1). The eruption was resistant to treatment with 0.1% triamcinolone cream by the child’s pediatrician. The patient also had a two-week history of hard, painful stools which often caused her to cry with bowel movements. Additionally, the patient’s head perspired frequently during sleep.

The patient’s mother had applied 0.1% triamcinolone cream for one week prior to her initial dermatology office visit. A trial of homeopathic calcium carbonate 30C p.o. BID was begun (Boironusa.com). Two days after beginning the homeopathic calcium carbonate, the mother discontinued the triamcinolone cream. At three weeks, the eruption had improved by approximately 50% in width and redness (Figure 2). Of note, the mother stated that the lichen striatus eruption initially became redder for the first week of therapy, and then it began to gradually fade. At 6½ weeks, the eruption had completely resolved without any postinflammatory hyperpigmentation (Figure 3). The mother related that the patient’s stools became softer and the toddler no longer cried with bowel movements. Also, the patient’s head perspired less during sleep.

No adverse effects occurred during treatment. The homeopathic calcium carbonate was well-tolerated by the infant with no adverse effects.

Discussion
Homeopathic medicine is a low-cost, nontoxic system of healing used by an estimated 500 million people worldwide. Homeopathic medicine uses microdoses of natural substances derived from plants, minerals, and animals for the purpose of stimulating the body’s natural healing response. The United States Food and Drug Administration recognizes homeopathic remedies as drugs and regulates their manufacturing, labeling, and dispensing. Homeopathic medicine was founded in the late 1700s by the German physician Samuel Hahmemann, MD. Classical homeopathic principles include: the law of similars (like cures like), the utilization of the smallest dose necessary, and the wholistic approach to the patient.3

The homeopathic calcium carbonate preparation that we used is commercially available over the counter from the Boiron company. It comes in a pleasant-tasting pellet which readily dissolves in the mouth. The 30C potency (strength) was prescribed in our case, and twice daily dosing was used. In infants, it is recommended that the two pellets are either crushed between two metal spoons and given as a powder or dissolved in 10 milliliters of drinking water. Homeopathic calcium carbonate was not specifically chosen for this patient because of her dermatological diagnosis of lichen striatus. Rather, it was selected because her clinical presentation was quite typical for the “calcium carbonate” patient type: the chubby, sweaty, constipated infant who craves milk. Additionally, these infants are often stubborn and inquisitive, and they move slowly and deliberately. Finally, our patient reached her developmental milestone for walking at 15 months of age, which is quite late on the late side – another typical “calcium carbonate” patient trait. The closer the patient’s signs and symptoms fit the chosen homeopathic medicine’s typical picture, the more likely clinical success will be.

It is possible that this patient’s lichen striatus resolved spontaneously. However, the patient’s localized hyperhidrosis and painful constipation also improved simultaneously with administration of calcium carbonate, suggesting treatment efficacy. A pilot study would be helpful to confirm the effectiveness of this inexpensive, over-the-counter homeopathic remedy in properly selected lichen striatus patients.

References
Case Report

We report the case of a full-term female who was noted to have new-onset linear lesions over her right thigh and right trunk on day three of life. The patient’s mother denied any trauma to the lesions. Pregnancy was complicated by hypertension but was otherwise unremarkable. Family history revealed that the patient’s half-brother has Down syndrome, but it was otherwise noncontributory. Dermatology was consulted for further evaluation.

On physical examination, multiple 2-4 mm, erythematous, firm papules were noted linearly along the right flank (Figure 1). Similar-appearing lesions tracked from the right groin down the medial leg to the right ankle (Figure 2). A 4 mm punch biopsy was performed on the right leg with a differential diagnosis of epidermal nevus versus IP. Pathology revealed spongiosis with chronic eosinophilia (Figure 3). The pathologic findings and early clinical presentation are consistent with IP. During the one-week follow-up for suture removal, the patient’s mother was examined with a Wood’s light, and no minor pigmented lesions were noted. The patient was referred to pediatric ophthalmology and pediatric neurology for further evaluation. To date, ophthalmologic and neurologic findings, including an EEG, are negative. After consultation with pediatric dermatology at the University of Missouri, it was felt that given her limited skin findings, involvement of other organ systems associated with IP would be unlikely in her lifetime. At the time this article was written, the patient continued to have a normal physical exam and was achieving all developmental milestones. The papules on the legs and trunk have regressed, and no new lesions are present.

Discussion

Incontinentia pigmenti (IP) is a rare genodermatosis defined in the 1920s by Bardach, Bloch, Siemens, and Sulzberger. It is a multi-system, ectodermal disorder often associated with ocular, dental, central nervous system, and skeletal abnormalities. Approximately 1 in 50,000 newborns is diagnosed with IP. The female to male ratio, female to female transmission, reports in males with karyotype 47,XXY (Klinefelter syndrome), and rare incidence in karyotype 46,XY males all support the suggestion that IP is an X-linked dominant disorder with lethality of males in utero. Lyonization (the inactivation of one of the two X chromosomes in women) seen in X-linked dominant disorders causes a functional mosaicism that results in the typical phenotype of IP. A mutation in NEMO, NF-kB essential modulator, gene on Xq28 is believed to play a role in the pathogenesis of IP. Mutated NEMO results in the defective activation of NF-kB, a transcription factor necessary for inflammatory, immune and apoptotic pathways.

The rare instances of IP seen in males may be due to one of three mechanisms: a high rate of de novo germline mutations, unstable premutations, and the half-chromatid hypothesis.

The diagnosis of IP is based on clinical examination. Cutaneous manifestations are the earliest signs and can be classified into four clinical stages. Stage I (vesicular) consists of inflammatory vesicles and bullae in a linear arrangement on the extremities, trunk and scalp. Erythematous macules and papules may also be present. Crops of blisters usually appear at or soon after birth, and each crop will clear within 1-2 weeks of onset. Stage I generally resolves by four months of age. Interestingly, blisters may recur during acute febrile illness in childhood. Stage II (verrucous) is marked by streaks of hyperkeratotic brown papules with pustules and papules on the extremities. Typically, lesions are seen from 2-6 weeks of life. Hyperkeratotic, warty lesions form as the blisters from stage I dry out. However, a report of IP beginning with hyperkeratotic lesions consistent with stage II has been reported. During a retrospective study of 40 children with IP, Hadj-Rabia et al. found one patient in whom stage I findings were absent, and the skin disease started with the presence of hyperkeratotic papules. In over 80% of cases, stage II lesions will clear within six months.

Stage III (hypermelanosis) is defined by macular, hyperpigmented swirls and streaks along Blaschko’s lines most apparent on the trunk. The slate-brown to blue-gray pigmentation, appearing as a “Chinese figure,” describes the most characteristic phase of IP. Stage III generally appears at around 3 to 6 months, after the blisters of stage I have disappeared. The distribution of stage III lesions is unrelated to the distribution of the previous vesicular rash. Hyperpigmentation may also be seen in the axillae, groin, and nipples. The majority of pigmented lesions will resolve by age 16; however, pigmentation may remain until the end of the second decade. Occasionally, especially in the groin, hyperpigmentation may be permanent.

Stage IV (hypopigmentation) is characterized by hypopigmented swirls best seen on the lower extremities. Follicular atrophy (pale, atrophic, hairless lesions) may or may not be seen. Known as the “burn out” stage of IP, lesions typically present during the second and third decades. Landy and Donnai support the observation that the hypopigmented lesions of IP are primarily related to decreased vascularity and a lack of hair follicles; changes in the amount of pigmentation is considered a minor contributory factor.

Additional anomalies, especially of the central nervous system, eyes and teeth, should be evaluated. Abnormal hair in IP tends to be wiry, course and lusterless. Scarring alopecia may be seen in up to 30% of cases. Up to 40% of cases are associated with dystrophic nail changes. Involvement is variable, ranging from nail pitting to severe nail disruption and involving all toenails and nails or only specific nails. Subungual tumors of IP (STIP) are a late manifestation of IP which tend to appear sometime after puberty, at 15 to 31 years old. STIPs may result in destruction to the distal phalanx by pressure necrosis of the underlying bone. Dental abnormalities occur in over 80% of patients. In contrast to the skin findings, dental features of IP are persistent throughout life. Typical features include: anodontia, conical teeth, delayed eruption and impaction. The hallmark of ocular IP is related to retinal ischemia. Abnormalities of the developing retinal vessels and the underlying pigmented cells are present in over 40% of patients. Diffuse hypopigmentation in the retina is a pathognomonic finding.
of IP. As many as 10% of patients may progress to intracranial scarring, resulting in loss of vision. Additional ocular associations include strabismus, cataract, optic atrophy and microphthalmos. Central nervous system disorders are seen in 30% of patients and include seizures, mental retardation and spastic paralysis. Up to 13% of patients with IP may have a convulsive disorder. Huber and Callen reported a case of IP that began with a seizure on day 1 of life followed by a vesicular rash on day 4 of life. Skeletal abnormalities (contractures, scoliosis and dislocations) and ear anomalies are also associated with IP. Landy and Donnai reported that all cases of structural abnormalities in their study were associated with mental retardation. Immunologic dysfunction may be present in IP patients. Cutaneous and pulmonary tuberculosis has been reported.

IP is diagnosed based on clinical features. Any condition which involves the lines of Blaschko can easily be confused with IP. In 1993, Landy and Donnai suggested strict diagnostic criteria to aid in making a definitive diagnosis. The criteria divide possible IP patients into two categories: those with evidence of IP in a first-degree female relative versus those without evidence of IP in a first-degree female relative. In a study by Hadj-Rabia et al., 28% of IP patients had a family history of IP involving at least the mother, while 62% of the patients were considered to have sporadic IP. If sporadic IP is being considered, then at least one of the four clinical stages of IP must be present as a major criterion for diagnosis. Supportive findings include dental involvement, alopecia, woolly hair, nail dystrophy, and retinal disease. Although the diagnosis of sporadic IP only requires one clinical stage of the skin manifestations, if supportive findings are not present, the possible diagnosis of IP should be made with a higher degree of uncertainty. When the patient is a female of an affected first-degree female relative, the diagnosis is made if any of the following are present: any clinical stage of the cutaneous manifestations, anomalous dentition, woolly hair, retinal disease, or multiple male miscarriages.

The detection of certain histologic features should also serve as major diagnostic criteria. During the neonatal period, keratinocyte apoptosis and eosinophilic spongiosis are characteristic of IP. Bullae form within a spongiotic epidermis, and the dermis shows inflammatory changes with numerous eosinophils (Figure 4). Lichenoid papules show hyperkeratosis, acanthosis and edema of the basal layer. The warty lesions of stage II show even more hyperkeratosis, and hyaline bodies representing individual cell keratinization are seen within the irregularly acanthotic epidermis. In stage III lesions or later, apoptosis and free melanin suggest the diagnosis of IP. The name incontinentia pigmenti is derived from this histological feature, where there is incontinence of melanin from the melanocytes into the superficial dermis. The only supporting laboratory datum for diagnosing IP is the existence of blood eosinophilia seen during infancy.

Many disorders should be considered in the differential diagnosis of IP, and the considerations will vary depending on the presenting stage of IP.

Patients with IP have a normal life span; however, having IP may increase the risk of developing a childhood malignancy due to chromosomal instability. Usually, treatment is aimed at controlling secondary infection. Systemic therapy with corticosteroids or sulfapyridine has not been found to be beneficial. Treatment is based on multidisciplinary collaboration, and the primary goal is to increase the detection rate of potential anomalies which may occur in early childhood or later in life. Patients should be seen by dermatology for diagnosis and proper management of skin findings. Examination of the mother, preferably with a Wood’s light, for pigmented anomalies is warranted to aid in the diagnosis. Blisters should be kept clean, dry, and protected from trauma. Reassurance that the rash will clear and patient education of future skin changes are the mainstays of dermatologic treatment. Subungual tumors presenting later in life should be treated. STIPs are typically treated with excision and curettage; however, oral etretinate has been reported to clear the tumors with continued resolution at 37 months.

At the time of diagnosis, all IP patients should be seen by an ophthalmologist. If neurological abnormalities are present, patients must be referred to a neurologist for further work-up. Referral to a dentist is recommended at one year of age. Genetic counseling, of both the patient and relatives, may be necessary to confirm or rule out IP. Affected women should be informed that they may have an increased rate of miscarriages and difficulty conceiving.

**Conclusion**

IP is a rare disease which affects many different organ systems. We describe a case of erythematous papules distributed in a linear arrangement along the lower extremity. Our patient presented with firm papules, appearing on day 3 of life, consistent with early stage 1 lesions of IP. Given the mother’s negative skin findings and the absence of family history for IP, the clinical picture is consistent with sporadic IP. Long-term and close communication between pediatricians, dermatologists, neurologists, ophthalmologists, dentists and even genetic counselors is crucial for a better understanding of IP in the future.

**References**


**Accessed June 20, 2010.**
History
A 45-year-old Caucasian male with no significant medical history presented to dermatology seven years prior. He presented with two 6 mm, asymptomatic yellow facial papules with peripheral telangiectasias of 10 months duration and a rapidly growing, solitary, fleshy, colored, crateriform nodule. Biopsy report was consistent with two sebaceous adenomas, and the third specimen showed a probable keratoacanthoma with sebaceous differentiation. Given the concern for Muir Torre syndrome, he was further questioned, and reported intermittent rectal bleeding. He was referred to gastroenterology. Colonoscopy showed an invasive adenocarcinoma of the colon with nodal involvement. He underwent a partial colon resection and chemotherapy. Genetic counseling and germline analysis confirmed Muir Torre syndrome.

He subsequently was found to have a liver lesion consistent with metastatic colon cancer and underwent resection as well as chemotherapy in 2007. Furthermore, in 2008 he had two isolated pulmonary metastases of colon carcinoma, which were resected.

On physical examination, multiple dome-shaped, yellowish papules were observed on the patient’s left cheek (Figure 1) and right upper back. A 1-cm pink nodule with a central hyperkeratotic plug was observed on the right temple (Figure 2). Histopathology was consistent with sebaceous adenoma (Figure 3), sebaceous carcinoma (Figures 4-5), and keratoacanthoma (Figure 6), respectively. Results of immunohistochemical studies performed on a sebaceous carcinoma revealed positive expression of MLH1 mismatch repair (MMR) protein, but absent expression of MSH2 and MSH6 protein (Figures 7-9).

After his diagnosis, he became aware that multiple paternal family members were afflicted with Muir Torre syndrome, including his father, who died of colon cancer at age 58. His son was also found to be carrying the same mutation.

Currently, he continues to develop multiple sebaceous adenomas, sebaceous carcinomas, keratoacanthomas, and squamous cell carcinomas. A summary of his medical conditions is shown in Table 1. The patient was unable to tolerate isotretinoin therapy to decrease the frequency of his lesions. His skin lesions have been surgically excised. He is followed by Gastroenterology, Oncology, and Dermatology.

Discussion
Muir Torre syndrome is a rare, autosomal-dominant disorder characterized by the presence of sebaceous neoplasms and/or keratoacanthomas with an underlying visceral malignancy. The most common visceral malignancies are colorectal and genitourinary tumors. It is believed to be a phenotypic subset of hereditary nonpolyposis colorectal cancer. It is caused by mutations in genes encoding for mismatch repair (MMR) proteins. We report a 39-year-old Caucasian male with a seven-year history of Muir Torre syndrome who continues to develop multiple sebaceous neoplasms, keratoacanthomas, and squamous cell carcinomas in association with colon cancer.

References
Figure 3: Sebaceous adenoma

Figure 4-5: Sebaceous carcinoma demonstrating atypical basaloid cells with prominent sebaceous differentiation and abundant sebaceous-type secretion centrally.

Figure 6: Acanthotic with central keratinous plugs and keratinocytes with glassy cytoplasm consistent with keratoacanthoma.

Figure 7: Sebaceous carcinoma demonstrating MLH1 protein expression.

Figure 8. Sebaceous carcinoma demonstrating lack of expression of MSH2 protein.

Figure 9. Sebaceous carcinoma demonstrating lack of expression of MSH6 protein.

Table 1: Medical History

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sebaceous adenoma</td>
<td>8/03, 6/06, 3/07, 5/09, 3/10</td>
</tr>
<tr>
<td>Cystic sebaceous adenoma</td>
<td>5/07</td>
</tr>
<tr>
<td>Sebaceous carcinoma</td>
<td>1/04, 3/08</td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>8/03, 1/04, 7/09, 12/09, 3/10</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>3/08, 4/08, 8/09, 10/09, 11/09</td>
</tr>
<tr>
<td>Right upper lobe resection secondary to two isolated pulmonary metastases of colon carcinoma</td>
<td>12/08</td>
</tr>
<tr>
<td>Right hepatic lobe metastatic colon cancer status post resection</td>
<td>9/07</td>
</tr>
<tr>
<td>Synchronous rectal / left sigmoid colon adenocarcinoma and right-sided, poorly differentiated invasive adenocarcinoma with nodes positive, status post resection</td>
<td>2003</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>Small-bowel polyps</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Diagnosis of Lynch syndrome

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 3 or more relatives with an associated cancer (colorectal, endometrial, small intestinal, or of the genitourinary tract)</td>
</tr>
<tr>
<td>2. 2 or more successive generations involved</td>
</tr>
<tr>
<td>3. 1 or more relatives diagnosed before the age of 50 years</td>
</tr>
<tr>
<td>4. 1 should be a first-degree relative of the other two</td>
</tr>
</tbody>
</table>
Case Report

A 48-year-old male presents with a well-circumscribed, slightly ulcerated lesion along the left ala that began seven months ago when his dog playfully scratched the area. The lesion “lasered” (presumably curettage) by a physician friend with no significant results. The patient states that he has chronic cervicogenic migraines due to irreversible nerve damage following a car accident that required orthopedic spine surgery with rod placement approximately five years ago. Twenty-six years ago, the patient suffered a severe burn on his torso, including both arms. He admitted to pouring 5 gallons of gasoline into a tar kettle without a funnel. The gasoline ignited when it hit the motor. The patient suffered spotted third-degree burns, particularly post zoster. Overexposure to radiation therapy for malignant transformation, including herpes zoster.

Comment

Marjolin’s ulcer is a malignant transformation of a posttraumatic area of skin, usually after a burn, that may occur as a chronic or acute type. Typically, the malignant transformation is squamous cell carcinoma (SCC), but basal cell carcinoma, malignant melanoma, and mesenchymal malignancy have been recorded sequela. The ulceration may range from a flat, non-healing wound with induration to a much more significantly elevated lesion that could also extend to the bone. Presented here is a 48-year-old male who came into the clinic following a non-healing lesion secondary to a dog scratch seven months prior. Biopsy revealed SCC and, upon discussing patient’s history was found to have sustained burns to the area over two decades prior. To the author’s knowledge, this is the second case of Marjolin transformation on the nose since the initial 2002 case.

References

10) Huang CY, Feng CH, Hsiao YC, Chuang SS, Yang JY. Burn scar carcinoma. J Dermatolog Treat. 2010 May;
Finacea is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been evaluated.

Finacea is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use. Finacea is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation. In clinical trials, sensations of burning/stinging/tingling occurred in 29% of patients, and itching in 11%, regardless of the relationship to therapy. Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure to the eye. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

Please see following page for brief summary of full Prescribing Information.


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Rx only

**BRIEF SUMMARY**

**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**INDICATIONS AND USAGE**

FINACEA Gel, 15%, is indicated for topical treatment of inflammatory papules and pustules of mild to moderate rosacea. Although some reduction of erythema which was present in patients with papules and pustules of rosacea occurred in clinical studies, efficacy for treatment of erythema in rosacea in the absence of papules and pustules has not been established. Patients should be instructed to avoid spicy foods, thermally hot foods and drinks, alcoholic beverages and to use only very mild soaps or soapless cleansing lotion for facial cleansing.

**CONTRAINDICATIONS**

FINACEA Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

**WARNINGS**

FINACEA Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral or intravaginal use. There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with skin complex, these patients should be monitored for early signs of hypopigmentation.

**PRECAUTIONS**

**General:** Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA Gel, 15%, treatment should be discontinued and appropriate therapy instituted.

In a transgenic mouse study, chronic use of FINACEA Gel led to an increased number of animals with papillomas at the treatment site (see PRECAUTIONS: Carcinogenesis, Mutagenesis, and Impairment of Fertility). The clinical relevance of the findings in animal studies to humans is not clear.

**Information for Patients:** Patients using FINACEA Gel, 15%, should receive the following information and instructions:

- **FINACEA Gel, 15%,** is to be used only as directed by the physician.
- **FINACEA Gel, 15%,** is for external use only. It is not to be used orally, intraocularly, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA Gel, 15%. Avoid alcoholic cleansers, tinctures and astringents, abrasives and peeling agents.
- Avoid contact of FINACEA Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA Gel, 15%.
- Cosmetics may be applied after FINACEA Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persistent use of FINACEA Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including sugar and alcohol), coffees, alcoholic beverages, and thermally hot drinks, including hot coffee and tea.
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occultive dressings or wrappings.

**Drug Interactions:** There have been no formal studies of the interaction of FINACEA Gel, 15%, with other drugs.

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

Systemic long-term animal studies have not been performed to evaluate the carcinogenic potential of azelaic acid. In a 26-week dermal carcinogenicity study using transgenic (Tg.AC) mice, FINACEA Gel, 15%, and the gel vehicle, when applied once or twice daily, did not increase the number of female Tg.AC animals with papillomas at the treatment site. No statistically significant increase in the number of animals with papillomas at the treatment site was observed in male Tg.AC animals after once daily application. After twice daily application, FINACEA Gel, 15%, and the gel vehicle induced a statistically significant increase in the number of male animals with papillomas at the treatment site when compared to untreated males. This suggests that the positive effect may be associated with the vehicle application. The clinical relevance of the findings in animals to humans is not clear.

Azelaic acid was not mutagenic or clastogenic in a battery of in vitro Ames assay, HGPSR in V79 cells (Chinese hamster lung cells), and chromosomal aberration assay in human lymphocytes) and in vivo (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

**Pregnancy:**

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicity studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 500 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits and cynomolgus monkeys.

An oral peri- and post-natal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose of level 500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the post-natal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study.

Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

**Nursing Mothers:** Equilibrium dialysis was used to assess human milk partitioning in vitro. At an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA Gel, 15%, is administered to a nursing mother.

**Pediatric Use:** Safety and effectiveness of FINACEA Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

**ADVERSE REACTIONS**

Overall, treatment-related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness, were 19% (24/124) for FINACEA Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks. In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity

<table>
<thead>
<tr>
<th></th>
<th>Vehicle (N=331)</th>
<th>Moderate Intensity</th>
<th>Moderate Moderate Intensity</th>
<th>Severe Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burning/stinging/tightening</td>
<td></td>
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<tr>
<td>Pruritus</td>
<td></td>
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<tr>
<td>Scaling/dry skin/erythema</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Erythema/irritation</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Contact sensitivities</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Edema</td>
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<tr>
<td>Acne</td>
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</tbody>
</table>

*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event. FINACEA Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis plana), and exacerbation of recurrent herpes labialis.

Post-marketing safety-Skin: facial burning and irritation; Eyes: indocytosis on accidental exposure with FINACEA Gel, 15%, to the eye (see PRECAUTIONS). Distributed under license: U.S. Patent No. 6,534,070 www.myfinacea.com

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Case Report

A 33-year-old Hispanic female presented to the dermatology clinic with a history of multiple “bumps” on the nose and surrounding the mouth. The patient first noticed these lesions 10 years prior, and since that time had noticed a significant increase in the number and size of the lesions. The patient had been treated by her primary care physician with prescription topical steroids prior to arrival in the dermatology clinic; however, these failed to produce results. The patient denied any pruritus, bleeding or pain associated with the lesions but was dissatisfied with the cosmetic appearance of the lesions. The patient was otherwise healthy with no significant past medical history. Interestingly, the mother and sister of the patient also had similar-appearing lesions on the face, while the two brothers remained unaffected.

Physical examination revealed a well-developed, healthy-appearing female in no apparent distress. Examination of the skin revealed multiple 1-5 mm, central facial, flesh-colored, non-tender papules overlying the nose, glabella, forehead, medial checks, nasal labial folds, upper lip, lower lip, and chin (Figure 1). The scalp, chest, back, abdomen, genitalia, and extremities remained lesion-free. Examination of the patient’s mother, at a later date, revealed similar-appearing lesions as described above, greater in number, and in the same distribution (Figure 2).

Initial shave biopsy was performed of an upper lip lesion, along with subsequent biopsies of the glabella and nasolabial fold. All three biopsies showed aggregations of basoloid cells, which formed cribriform patterns and displayed signs of follicular differentiation within the dermis. The stroma was highly fibrotic and resembled that of an embryonic perifollicular sheath. Horn cysts were also noted within the lesion, all consistent with trichoepithelioma (Figure 3).

Additional biopsies obtained from the patient’s mother at the nasal bridge demonstrated well-circumscribed aggregations of epithelial cells arranged in interweaving cords present within the dermis. There were cells with small, dark nuclei at the periphery of the cords, and cells with large, pale nuclei in the center of the cords. Globules of homogenous eosinophilic material were also present within the aggregations, all findings suggestive of spiradenoma (Figure 4). Given the clinical history, family history, and histopathology obtained, the working diagnosis of Brooke-Spiegler syndrome was made.

To date, both the patient and her family members have been educated regarding the disorder. Several of the larger, more cosmetically disfiguring, trichoepitheliomal lesions on the face have been removed with shave biopsy. As the patient remains asymptomatic, the plan is to monitor the lesions for malignant transformation and continue with the removal of the remaining lesions at the patient’s discretion.

Discussion

Brooke-Spiegler syndrome (BSS) is a rare condition consisting of multiple cylindromas, spiradenomas, and trichoepitheliomas, inherited in an autosomal-dominant fashion with variable penetrance and expressivity amongst family members. Adnexal neoplasms such as trichoblastomas, basal-cell carcinomas, and malignant transformation of pre-existing tumors have also been associated with this disease state. Lesions typically appear within the second decade of life, increasing in size and number with time.1,2

The pathogenesis of BSS has been linked to various mutations in a tumor-suppressor gene, CYLD, located on the chromosome 16q12-q13. To date, 51 germline mutations have been reported, demonstrating that various mutations in the same patient can result in tumor formation of the same histologic subtype. Of note, phenotypical features of the differing adnexal-subtype neoplasms are related to the same genetic defect.3,4,5

Clinically, patients often present with multiple, small, flesh-colored papules, most frequently located on the face and neck. Lesions appearing on the scalp, likely cylindromas, can multiply, coalesce, and result in partial or complete hair loss. These areas are referred to as turban tumors.1,2 Though usually benign, the cylindromas have been documented to undergo malignant transformation. Patients affected by this condition are also at risk for the development of basal-cell adenomas and adenocarcinomas of the parotid and minor salivary glands. Therefore, continued surveillance along with patient education regarding ulcerations or changing features of the lesions is prudent. To note, BSS has also been documented in association with pegged teeth and unilateral hearing loss.6,7 A definitive diagnosis is made with biopsy. One should consider the diagnosis of BSS if a patient presents with multiple lesions and biopsy-proven tumors including spiradenoma, cylindroma, and trichoepithelioma. Histologic examination of lesions varies dependent on tumor type. Spiradenomas appear multinodular with a trabecular pattern and scattered lymphocytes within each nodule. The nodules are composed of poorly differentiated basoloid cells. Cylindromas consist of basoloid cells arranged in a jigsaw-like pattern. Surrounding each nodule is an eosinophilic, PAS-positive basement membrane. Trichoepitheliomas classically are composed of clusters of follicular germinative cells with evidence of superficial follicular differentiation and small keratinizing cystic spaces.1

Treatment of the patient with BSS traditionally consists of tumor excision, dermabrasion, electrodessication, cryotherapy, and laser therapy with the argon or CO2 lasers, with a goal to enhance the cosmetic appearance. Frequent surveillance of lesions becomes important to monitor for malignant transformation.

References


FESER, BETHEA, GREKIN 51

Christina L. Feser, DO,* William A. Bethea, DO,** Steven K. Grekin, DO***
*Dermatopharmacology Fellow, Haber Dermatology and Cosmetic Surgery, Inc., Cleveland, OH
**PGYII Dermatology Resident, Oakwood Southshore Medical Center, Trenton, MI
***Program Director, Department of Dermatology, Oakwood Southshore Medical Center, Trenton, MI

ABSTRACT

Brooke-Spiegler syndrome (BSS) is a rare condition, inherited in an autosomal dominant fashion, which is characterized by multiple cylindromas, spiradenomas, and trichoepitheliomas. The lesions of BSS are known to most commonly affect the face and neck. Though usually benign, lesions of BSS have been documented to undergo malignant transformation. Awareness of this condition is important to accurately diagnose, manage, and continue with close surveillance of patients affected by this disorder.

FESER, BETHEA, GREKIN 51
**NEW WORLD LOCALIZED CUTANEOUS LEISHMANIASIS: A CASE REPORT**

Damian Sacky, OMS-IV,* Brent Loftis, D.O.,** Bill V. Way, D.O., FAOCD***
*OMS-IV, University of North Texas Health Science Center – Texas College of Osteopathic Medicine, Fort Worth, TX
**Dermatology Residency Program Director, Dermatology Institute, Northeast Regional Medical Center Department of Dermatology, Kirksville College of Osteopathic Medicine – Texas Division, Duncanville, TX
***Dermatology Residency Program Director, Dermatology Institute, Northeast Regional Medical Center Department of Dermatology, Kirksville College of Osteopathic Medicine – Texas Division, Duncanville, TX

**ABSTRACT**

Leishmaniasis encompasses a spectrum of diseases caused by multiple species of the parasitic protozoan Leishmania, with clinical presentations varying from localized skin lesions to systemic disease. The most common clinical syndrome within this spectrum is cutaneous leishmaniasis, whose presence in the United States is traditionally associated with foreign travel or occupational exposure. However, it is considered to be endemic in southern Texas, and there is growing concern about its increased incidence in northern Texas. We present an autochthonous case of cutaneous leishmaniasis involving a 76-year-old Caucasian female from north Texas who was referred to our dermatology clinic for evaluation of a pruritic lesion on her left cheek. This case report serves to elevate the physician's index of suspicion when evaluating unknown skin lesions and add to the body of knowledge that exists about cutaneous leishmaniasis infections in the state of Texas.

**Introduction**

Leishmaniasis is a parasitic disease that is most commonly transmitted via the bite of infected female sand flies. It is disseminated globally, occurring mainly in developing countries, and is responsible for a wide array of clinical syndromes, the most common of which is cutaneous leishmaniasis (CL). With regard to the United States, infections with leishmaniasis are rare and are regularly associated with occupational exposure or a travel history to areas where leishmaniasis is endemic. However, it is known that the species Leishmania mexicana is endemic in south Texas, with the Lutzomyia spp. sand flies being the vector. In recent years, autochthonous cases of CL have appeared in areas outside of the established endemicity range of L. mexicana. We present an autochthonous case of CL diagnosed in a north Texas resident.

**Case Report**

A 76-year-old Caucasian female, who resides in a city located near the Dallas-Fort Worth Metroplex, was referred to our clinic by her primary care provider to evaluate a pruritic lesion on her left cheek of a six-week duration. The patient stated the lesion was of an insidious onset and gradually increased in size without any other accompanying changes. She denied having attempted to treat the area with home remedies or other medications. The patient's past medical history included hypertension and hypothyroidism, both under control; otherwise, the patient was healthy, with no evidence of being immunocompromised. Her medications included ramipril, furosemide, labetalol, valsartan, vaginal estrogen, fluconazole, prednisone, omeprazole, naproxen, melanotan, and multiple vitamins and minerals. The patient denied having any known drug allergies. The rest of the patient's medical history was non-contributory.

Physical examination of the skin revealed a single, erythematous, 6 mm x 13 mm, indurated nodule without ulceration on her left cheek (Figure 1). Further examination of the skin was unremarkable and revealed no significant findings. Our differential diagnosis included basal cell carcinoma, angiosarcoma, Merkel cell carcinoma, and cutaneous lymphoma. A 4 mm punch biopsy of the nodule was performed and was sent for pathology. The patient subsequently returned the following day concerned about ecchymosis around her left eye. However, this visit proved unremarkable, and the patient was reassured that this was common and that it would resolve.

Histopathologic examination of the biopsy revealed skin with a dermal nodular granulomatous inflammatory infiltrate (Figure 2). At higher power there are collections of epithelioid histiocytes with ill-defined granulomas and a background lymphoplasmacytic infiltrate (Figure 3). Small organisms are noted at high power within the macrophages and lining cystic spaces (marquee sign). The organisms are small, round-to-oval basophilic structures, 1-2 microns in size, some with visualized diagnostic kinetoplasts (Figure 4).

Subsequent to our diagnosis of localized cutaneous leishmaniasis (LCL), the patient and the Centers for Disease Control and Prevention (CDC) were contacted. In discussing the diagnosis with the patient, she stated it had been several years since she last traveled outside of the state of Texas and could not recall any other significant details related to the diagnosis at the time. Armed with this patient information, but without a biopsy specimen, the CDC stated the most likely organism is Leishmania mexicana and recommended treating this patient with topical 2% ketoconazole cream. It was to be applied to the affected area twice daily until noticeable improvement in the lesion, at which time treatment could be reduced to a once-daily application until complete resolution of the lesion.

The patient consented to this treatment, and in the meantime the hematoxylin and eosin (H&E) slides were sent to the CDC for review. CDC was contacted again to ensure they had received the slides for their review. At this time, after further communication, they recommended treating the patient with oral ketoconazole for six weeks, followed by a maintenance dose of 200 mg twice a week until complete resolution of the lesion.

**Discussion**

Leishmaniasis is a disease that has been remarked on throughout history, possibly as early as 2000 BCE, and has been called by several different names. When W.B. Leishman and Charles Donovan independently identified the protozoan parasite responsible for this disease, they published their findings in 1903, and afterwards Ronald Ross identified this new genus as Leishmania. Subsequently, over 20 species of Leishmania have been identified, and the phlebotomine sand fly has been recognized as the predominant insect vector.

Today there is no question of its worldwide impact, with as many as 350 million people at risk for contracting this disease and with some two million new cases yearly. Long considered a neglected disease, it has garnered enough attention for international authorities to implement policy in an attempt to curtail its impact. In general, leishmaniasis can be classified first by its geographic distribution, Old World (i.e., Africa, Europe and Asia) versus New World (Latin America and North America).
to growth of amastigotes in culture. However, routine histopathologic evaluation alone can miss the diagnosis of leishmaniasis in almost 80% of cases. Additional tests include the use of polymerase chain reaction (PCR) to identify leishmanial DNA, which offers the added benefit of a species-specific diagnosis, but also has certain limitations in chronic skin lesions with a low or absent inflammatory burden. Therefore, it is appropriate to utilize all of these methods in order to reach a trustworthy diagnosis. For physicians in the United States, the Parasitic Diseases branch of the CDC provides assistance with the laboratory diagnosis of CL, which is an invaluable service.

The CDC will tailor its approach to each individual case and will provide its services, including provision of culture mediums, free of charge. They examine specimen slides that have been prepared locally or at the CDC, culture and perform PCR, and will even do serologic testing all in the name of maximizing sensitivity and specificity for the diagnosis of CL and species identification. A detailed guide with step-by-step instructions on how to obtain aspirates and dermal scrapings is available on the CDC website and is recommended reading regardless of whether a biopsy has already been taken.

Treatment is tailored to the specific Leishmania subspecies with special consideration given to the side effect profile and cure rate of the chosen treatment. The overall goal of treatment for any leishmaniasis infection is to promote healing, reduce the risk of secondary bacterial infection and scarring, and prevent chronic disease. While it is less common for New World CL to spontaneously heal, LCL caused by the L. mexicana species is typically non-life threatening and self-resolving. Regardless, pentavalent antimonials such as sodium stibogluconate remain the standard treatment for CL. The current recommendation for this systemic agent’s use to treat New World CL due to L. mexicana is 20 mg/kg/d IM/IV for 20 days. Studies have found that a 10-day course is equally effective and less toxic; however, the growing concern for drug resistance has kept the current recommendation at 20 days. In cases where an L. mexicana infection is unlikely to progress to MCL, a topical application of 15% paromomycin/12% methylbenzothiazole applied twice daily for 20 days can serve as an alternative treatment when pentavalent antimonials are not freely available.

While vaccination leading to prevention of all forms of leishmaniasis is the ultimate goal, there is no Food and Drug Administration (FDA) approved vaccine currently. In the United States there is the additional challenge of obtaining sodium stibogluconate, since it is not commercially available and requires approval from the CDC and potentially other organizational authorities. So far, other possible treatments include drugs and modalities needing further evidence substantiating their safety and efficacy. With regards to specific Leishmania species, these include immune modulators, recombinant IFN, monoclonal antibodies, therapeutics, cyclosporine and azoles.

Historically, the south central region of Texas has been considered endemic for L. mexicana with the woodrat Neotoma micropus acting as its host. N. micropus has been traditionally recognized as the only known reservoir of Leishmania in the state with a defined habitat; however, in the last decade more cases of CL have cropped up outside of its known range north in Texas. It was a surprise that our patient was diagnosed with LCL considering the lack of travel history to areas outside of the U.S. well-known for Leishmania endemicity. However, it is unknown whether or not the patient traveled to nearby Texas counties with a known distribution of N. micropus. Given the variety of factors in play, such as the actual sand fly distribution, new Neotoma species implicated as hosts, and human sprawl, the true cause of these north Texas CL cases, and the actual distribution in the rest of the United States, have yet to be identified. In any case, physicians around the state of Texas should keep the diagnosis of CL on their differential diagnosis radar and know that the CDC can be an invaluable asset in the diagnosis and treatment of this disease.

References

The diagnosis of NF-1 is established if two of seven criteria are met (see Table 1).12 DeBella et al. determined that by eight years of age, 97% of NF-1 patients had met this criteria, and 100% had met the criteria by age 20.7

Multiple café-au-lait macules are suggestive of NF-1. However, single or few café-au-lait macules are a common, normal finding in the general population. As the patient ages, these lesions increase in size and number. Café-au-lait macules are also observed in Fanconi anemia, McCune-Albright syndrome, tuberous sclerosis and other syndromes (see Table 2). An increase in the density of melanocytes is noted in NF-1 patients with café-au-lait macules compared with those who have isolated café-au-lait macules without NF-1 involvement. Schwann cells, mast cells and fibroblasts make up the benign neurofibroma, which is another diagnostic finding in NF-1. Dermal and subcutaneous neurofibromas arise from peripheral nerves and usually form at the onset of puberty. They can be soft or firm and possess a pathognomonic buttonhole invagination when palpated. Plexiform neurofibromas are another subset with significant vascularity originating from multiple nerve bundles forming anywhere in the body and are a pathognomonic finding in NF-1. These have the potential for malignant transformation.6 Those diagnosed with NF-1 may also develop freckling to the inguinal region or the axillae, which is known as Crowe’s sign. Other cutaneous findings associated with NF-1 include juvenile xanthogranuloma, glomus tumors, melanoma, blue-red macule, pseudoatrophic macule and nevus anemicus.

There is a multitude of systemic manifestations seen in patients with NF-1, including Lisch nodules, benign, yellow-brown, hamartomaticus nevi affecting the iris that are best viewed upon examination with a slit lamp. Neurologic and learning disabilities are common. NF-1 patients with microdeletions have been reported to suffer more learning disabilities than those with isomorphic mutations.7 Coswyn et al. and Thompson et al. have reported significant findings of speech and articulation problems.9 In addition to scoliosis and dysplasia, other orthopedic complications can result from NF-1. There is an increase in bone resorption in NF-1 children, leading to osteopenia and osteoporosis.10 Other disorders linked to NF-1 include pheochromocytoma, vascular stenosis and macrocephaly.

Other types of neurofibromatosis include a type 2 and a segmental NF-1. Type 2 neurofibromatosis is characterized by eighth-nerve masses, neurofibromas, meningiomas, gliomas, schwannomas and juvenile subcapsular lenticular opacities. Due to the significant neurologic findings, the cutaneous aspect seldom aids the diagnosis of NF-2, and as a result it has a significant increase in morbidity compared to type 1. Segmental NF-1 skin findings are localized to a particular region of the body, and they are not at risk for neurofibromatosis-related disorders in the other, unaffected body regions.

Management of NF-1 consists of recognizing and differentiating it from other diseases, providing the necessary referrals and possible removal of cutaneous neurofibromas. The multidisciplinary approach involved with these patients should include a routine follow-up with a primary care physician, ophthalmologist, neurologist and dermatologist. Further referrals for symptomatic patients can include an orthopedist, oncologist, surgeon, endocrinologist and psychiatrist.

Spitz offers some additional guidelines and pearls: At a minimum, a baseline ophthalmologic examination should be performed. Exams should be annual for the next six years and then performed every two years. A blood pressure should be performed to consider renal artery stenosis or pheochromocytoma if elevated. Observing multiple juvenile xanthogranulomas should lead the practitioner to order a CBC because of the association with nonlymphocytic leukemia. A central-nervous-system tumor should be considered if a child presents with early puberty. Large café-au-lait lesions need to be palpated carefully for evidence of an underlying plexiform neurofibroma.11

The role of the MRI is important in evaluating symptomatic neurologic deficits. Neuroimaging should not be part of the assessment in the absence of ophthalmologic or other neurologic findings. A screening MRI in asymptomatic children in search of optic pathway gliomas is recommended by the Children’s Tumor Foundation.12 A recent study in France by Blanchard et al.
concluded that a screening MRI wasn’t useful because of the lack of any improvement in the therapeutic decision-making for asymptomatic optic gliomas in NF-1 children.\textsuperscript{13}

Though current pharmacological treatments are limited for the treatment of neurofibromatosis, a recent increase in drug trials related to controlling cell proliferation may provide therapeutic insight into the etiology of the disease. One promising trial described the use of specially formulated doxycycline to treat dermal neurofibromas. Its action causes vascular disruption, leading to necrosis and eventual skin clearing in a matter of days after injection.\textsuperscript{14} The same authors also discussed another trial using the monoclonal antibody ranibizumab to achieve the same clinical effects as doxycycline for dermal neurofibromas. There are other therapeutic avenues being explored. HMG-CoA reductase inhibitors such as simvastatin and lovastatin are thought to help increase cognitive function in patients with NF-1, but no trial has successfully proven these results.\textsuperscript{14,15}

Proper patient and family counseling concerning the nature and prognosis of the disease, with attention to psychosocial adjustment, should be provided. Patients should be reminded to use sunscreen routinely as a way to counteract the slight increase in risk of cutaneous malignancies as well as prevent darkening of the café-au-lait macules.

NF-1 patients require special attention to their various clinical manifestations. Treatment may often be challenging because of the involvement of multiple complications secondary to their vast sequelae, and a multidisciplinary approach is encouraged.

Dermatologists are often the frontline of diagnosis of neurofibromatosis. Therefore, early recognition and prompt referral to the appropriate specialists are necessary for the proper management of this disease. The prognosis of some of these conditions can be improved with timely intervention. Even though there is no cure for NF-1, the future looks hopeful in terms of decreasing the involvement of multiple complications secondary to their vast sequelae, and a multidisciplinary approach is encouraged.

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References

4. National Institutes of Health Diagnostic Criteria for NF1\textsuperscript{11}

Establish two of the seven criteria for NF1 Diagnosis

- Six or more café au lait macules
- 15 mm or greater in postpubertal individuals
- 5 mm or greater in prepubertal individuals
- Freckling in the axilla (Crowe sign) or inguinal region
- Two or more neurofibromas or the presence of a plexiform neurofibroma
- Two or more Lisch nodules
- An optic glioma
- One or more of the following bone abnormalities:
  - Sphenoid wing of the skull dysplasia, scoliosis or thinning of the long bone cortex
- First-degree relative with these NF1 criteria

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Case Report

A one-week-old, full-term, Afro-Caribbean female was taken to the emergency room secondary to concerns of progressively enlarging, erythematous, non-tender eruption present on her right cheek that had been present for two days and worsening. The patient's mother reported that the infant did not exhibit any fever, irritability, cough, vomiting or diarrhea. She was feeding and voiding well. The patient was admitted for a work-up and evaluation of facial erythema.

On physical, the infant presented with a red, warm, +/- tender, facial erythema and edema in a well-appearing, term, well-appearing infant in no acute distress.3 A complete skin exam including the facial eruption and transported the infant to a community hospital. The infant was admitted for work-up and evaluation of facial erythema.4 The infant was delivered via C-section after a 39-week gestation by a GBS+ mother. On her first day of life, the infant was transferred to a regional children's hospital for evaluation and treatment of supraventricular tachycardia. After five days in the hospital, just prior to discharge, the patient's mother noted an eruption on the patient's right cheek. The eruption was diagnosed as neonatal acne, and the patient was discharged home.

Two days after discharge, the patient's mother grew increasingly concerned about the facial eruption and transported the infant to a community hospital. The infant was admitted for work-up and evaluation. On physical, the infant presented with a 5 cm x 5 cm, bright red, erythematous, edematous, and indurated plaque covering her whole right cheek up to the ear (see Fig. 1). The oral mucosa was not involved, and no other plaques were found on her body. The remainder of the physical exam was unremarkable. The initial lab work was as follows: CBC with WBC = 11.9; hb = 15.6; hct = 47.8; plt = 309; CRP < 0.2; BMP was unremarkable with a normal calcium of 9.5 mg/dl. A full sepsis work-up including blood and cerebral spinal fluid cultures. The organisms implicated in bacterial facial cellulitis include: late-onset group B streptococcal (GBS) infection, Haemophilus influenza type B, Staphylococcus aureus, group A beta hemolytic streptococcus, Streptococcus pneumoniae, and Mycoplasma hominis.1,2 Late-onset GBS was strongly considered in light of maternal GBS+ history. Hauger et al. described how facial cellulitis can be an early indicator of GBS bacteremia with no fever on presentation.3

When the clinical presentation is atypical or the patient does not respond to appropriate therapy for cellulitis due to the routine pathogens, the differential diagnosis should expand. Our differential diagnosis expanded from bacterial cellulitis to deep hemangiomata, subcutaneous fat necrosis, cold panniculitis, and sclerema neonatorum. Despite appropriate antibiotic coverage, the infant's erythema did not resolve. The acute onset of the facial erythema and edema in a well-appearing, afebrile infant with no laboratory abnormalities and with negative cultures after 72 hours discounted the possibility of an infectious process.

The physical exam was revisited with a global assessment of the patient, a full-term, well-appearing infant in no acute distress. Based on the infant's healthy clinical appearance, sclerema neonatorum was not suspected. Sclerema neonatorum is a serious and often fatal disorder of adipose tissue that presents in gravely ill preterm infants with yellow-white, woody induration.3 A complete skin exam including lymph node examination was performed. No lymphadenopathy found. When focusing on the affected area, the color, morphology, and secondary changes and distribution of erythema were key features to note. The evolution of the lesion from an erythematous, edematous, indurated plaque into a bruise-like, violaceous, lobular, indurated plaque is consistent with the clinical appearance of both subcutaneous fat necrosis and cold panniculitis. A detailed review of the infant's past medical history revealed that the baby had ice pack application to the face for supraventricular tachycardia on her first day of life. Cases of subcutaneous fat necrosis and cold panniculitis have been reported following ice pack application and most often secondary to perinatal distress or hypothermia.3

Subcutaneous fat necrosis of the newborn (SCFN) is a rare disorder of the panniculus characterized by firm, erythematous nodules and plaques over posterior trunk, arms, buttocks, thighs and cheeks occurring within the first few weeks of life of full-term infants.3,4 Afflicted infants usually appear well and are afebrile. The condition begins as edema and then progresses to circumscribed nodules and plaque with an indurated feel. Although the exact pathogenesis is not known, maternal and perinatal factors have been implicated, including gestational diabetes, preeclampsia, maternal hypertension, maternal cocaine abuse, familial risk factors for thrombosis, birth asphyxia, cord accidents, hypothermic cardiac surgery, hypoxia, hypothermia, hypoglycemia and birth trauma.3,4 Neonatal fat comprises more saturated fatty acids (e.g., stearic and palmitic acids) than does adult fat. These saturated fatty acids have a relatively high melting point and undergo crystallization with hypothermia during neonatal stress.5 SCFN is often benign and self-limited, and the most important concern is the potential to develop hypercalcemia, which can lead to neurologic or cardiac problems, nephrocalcinosis and nephrolithiasis. The hypercalcemic phase, if it occurs, usually is observed during the resolution of the panniculitis, but these events may occur concomitantly.7 Histologically, the lesion shows a lobular panniculitis sparing the epidermis and dermis with mixed inflammatory cell infiltrate composed of histiocytes, lymphocytes, neutrophils and eosinophils.4 Needle-like clefts in radial configuration are seen in giant cells and lipocytes (see Fig. 3). A similar clinical presentation of erythematous, indurated plaque is seen with cold panniculitis. Cold panniculitis is the

**ABSTRACT**

We present a case of a newborn that developed supraventricular tachycardia shortly after birth and thereafter developed an erythematous eruption on the right cheek that progressed to a violaceous, indurated plaque. The diagnostic considerations and work-up of the infant with a red-to-violaceous facial indurated plaque are discussed.
result of prolonged exposure of any area of the skin to a cold object. The pathogenic mechanism of cold panniculitis is similar to SCFN in that the neonatal fat composition of increased saturated fatty acids seems to also play a role in its etiology.6,9 The most common sites of involvement of cold panniculitis are the cheeks, but it may be seen elsewhere. The induration resolves within a period of approximately two weeks, often leaving some post-inflammatory hyperpigmentation.9,10 No treatment is required. Histologically, cold panniculitis consists mostly of lobular panniculitis, with the most intense inflammation at the dermosubcutaneous interface. A reaction pattern of lymphocytes and histiocytes infiltrating fat lobules, along with a superficial and deep, perivascular, dermal infiltrate with no vasculitis, is characteristic (see Fig. 4a and 4b).10

A biopsy was not performed because the infant appeared well and the results of clinical history were consistent with cold panniculitis. But, without a histopathological confirmation, SCFN could not be ruled out. Even though the infant’s serum calcium during the hospital stay was normal, recommendations were given to monitor the infant’s serum calcium and symptoms of hypercalcemia for a minimum of six months.

Conclusion
A complete history and systemic and ongoing physical examinations are important steps in assessing any patient to arrive at a correct diagnosis. When considering the diagnosis of a neonate presenting with an indurated, erythematous plaque on a cheek, life-threatening infection (bacterial cellulitis) or illness (sclerema neonatorum) must first be ruled out. Cold panniculitis should be considered in the differential diagnosis of any neonate presenting with an indurated cutaneous plaque after undergoing ice-pack therapy. Clinicians need to be aware of the clinical similarities of cold panniculitis and SCFN and the histopathological diagnostic characteristics that distinguish them in order to counsel on potentially serious sequelae.

References
In this document we will discuss an interesting case of Epidermodysplasia Verruciformis and review pertinent genetic predisposition, differential diagnosis, to Human Papilloma Virus. We present a case of a 65 year old Caucasian male who presented with a chief complaint of asymptomatic papules on his arms and legs for approximately three years. After clinical work-up and biopsy, the histopathological changes were consistent with Epidermodysplasia Verruciformis. In this document we will discuss an interesting case of Epidermodysplasia Verruciformis and review pertinent genetic predisposition, differential diagnosis, diagnostic evaluation and treatment. In addition, we will discuss other Human Papilloma Virus infections with high malignant potential.

CASE REPORT

A 65-year-old Caucasian male presented with a three-year history of asymptomatic papules on his bilateral upper and lower extremities. The initial lesion emerged on the dorsal left forearm, followed by the right upper extremity and eventually bilateral lower extremities. The lesions were asymptomatic and stable in size, shape, and color. He denied having similar lesions in the past, trauma to the affected area or history of recent cutaneous infection or known malignancy. His primary care physician referred the patient to dermatology for further evaluation and management. Of note, the patient received no treatment prior to the referral.

The patient’s past medical history was significant for asthma, latent tuberculosis, osteoarthritis, and dyslipidemia. The past surgical history included bilateral knee arthroscopy. His current medications included Advair, oral vitamin D supplement, Trilipix, allopurinol and nabumetone. He reported an allergy to penicillin, which results in diffuse rash and airway edema when ingested. The patient admitted to occasional alcohol consumption and daily tobacco use, but denied recreational drug use. He denied travel outside the country and any outdoor hobbies.

Physical Exam

On physical examination, the patient appeared to be alert, oriented and in overall good health. He had Fitzpatrick type II skin, with usual signs of solar and chronological aging. Head, neck and trunk were unremarkable. Inspection of the limbs demonstrated dusky erythematous-brown papules ranging in size from 4mm – 11mm in diameter. Some of the lesions showed mild hyperkeratosis, while others were firm to palpation with a smooth surface texture. No surrounding erythema, edema or purulent discharge was noted. In addition, no necrosis or ulceration was observed.

A clinical differential diagnosis of diffuse verruca vulgaris, epidermodysplasia verruciformis, prurigo nodularis, nodular amyloid, perforating disease and cutaneous manifestation of hematologic malignancy was ascertainment. Due to the extensive differential diagnosis, a deep shave biopsy was performed on the right dorsal forearm.

The pathology report revealed a diffused epidermal hyperplasia with dilated tortuous capillaries in the papillary dermis. Within the spinous and granular cell layers were collections of keratinocytes with prominent blue-gray cytoplasm. Dysplastic or carcinomatous transformation was not seen. The diagnosis of Verruca vulgaris with viral cytopathic changes consistent with epidermodysplasia verruciformis (EDV) was made.

Due to the lesions’ susceptibility to carcinomatous conversion, a combination treatment regimen was initiated. First and foremost, counseling and education was provided to the patient on the etiology and longevity of EDV. The patient was instructed to monitor the skin for new lesions or any significant change in a pre-existing lesion. The importance of strict sun avoidance and protection was stressed. In addition, a full-body skin exam was performed, and biannual follow-up full-body skin exams were recommended. A combination of cryotherapy and topical 5-fluorouracil was also initiated for the destruction of current lesions. Thus far, the patient has been compliant with treatment and follow-up. No malignant transformation has been found, but continual surveillance is ongoing.
oncogenic catalyst on HPV-involved hair follicles. Inadequate DNA repair mechanism or inability to undergo apoptosis predisposes patients to cutaneous malignancies. It is no surprise then that EDV skin lesions are infrequently reported on non-sun-exposed areas. Decreased immune surveillance also explains why renal transplant recipients and immunosuppressed patients are at increased risk of developing diffuse EDV lesions.

Genetically predisposed individuals will often seek medical evaluation for multiple persistent verrucous lesions. Typically, the initial lesions that EDV patients develop are multiple flat, scaly macules on the face, trunk, neck, or dorsal hands that can mimic pityriasis versicolor. They can also present with verrucous papules that often appear on the dorsal hands. Typically, EDV lesions do not regress, and they are often refractory to standard treatment. It is very important to accurately identify EDV lesions since 30-70% of patients will go on to develop cutaneous squamous cell carcinomas after the third decade of life.

The differential diagnosis for a patient with EDV is tinea versicolor, squamous cell carcinoma, acrokeratosis verruciformis, prurigo nodularis, perforating disorders, pityriasis alba, vitiligo, drug eruptions, secondary syphilis, erythema multiforme, tinea corporis, and guttate psoriasis. Definitive diagnosis relies on the clinical picture and biopsy with characteristic pathologic findings. Histopathologic findings will vary depending on the HPV serotype involved. Some may look exactly like plane warts. However, EDV-associated HPV infections characteristically show large cells with perinuclear halos, in nests, located in the granular and spinous layers. The nucleoplasm is clear, and the cytoplasm is a blue-gray containing keratohyaline granules of various shapes and sizes. If questionable clinical picture or histopathologic findings occur, PCR-based methods to detect EV-HPV types should be performed.

Treatment for EDV is multifocal. Patients should be educated on strict sun protection or avoidance. They should be instructed to meticulously check for new lesions or significant changes in ones that have been previously identified. Furthermore, frequent physician evaluation is recommended to ensure prompt management of suspicious lesions. From there, treatment should be guided by the clinical presentation, which may vary over the course of a lifetime. There are no definitive treatments for EDV-HPV lesions. They are usually treated via destructive measures used in other non-EDV related HPV infections. The modality of treatment depends on the size, distribution, and histopathologic changes of the specific lesions. Methods consist of topical 5-FU, topical imiquimod, retinoids, cryotherapy, photodynamic therapy, and surgical excision. In recent reports, 0.5-1mg/day of acitretin has been effective and is arguably the drug of choice. If highly malignant transformation does occur, Mohs micrographic surgery is recommended for maximal removal of cancer with conservation of surrounding tissue. Tissue sparing may become particularly important for patients with numerous malignant lesions and high risk of recurrence.

Conclusion

This case presents a patient with clinical and histopathological findings consistent with epidermodysplasia verruciformis. Epidermodysplasia verruciformis is rare disorder distinguished by an extreme predisposition to wide-spread human papilloma virus infection and the development of squamous cell carcinomas. This susceptibility can be attributed to gene defects in the EVER1 and EVER2 genes, which leads to a decrease in cell-mediated immunity. We hope this case, along with the review of the literature, will aid in the clinical recognition, diagnostic work-up and management of patients with epidermodysplasia verruciformis.

References

**BIRT-HOGG-DUBÉ SYNDROME - A REPORT AND REVIEW OF ORIGINS, DIAGNOSIS AND MANAGEMENT**


* 3rd-year Resident, KCOM – Texas Division, Duncanville, TX
** OMS-IV, Nova Southeastern University, Fort Lauderdale, FL
*** Private Practice Dermatology, Fort Worth, Texas
**** Program Director, KCOM – Texas Division, Duncanville, TX

**ABSTRACT**

Birt-Hogg-Dubé Syndrome is a rare autosomal dominant genodermatosis featuring the prominent cutaneous finding of facial fibrofolliculomas. BHD has some significant internal associations as well, namely lung cysts, recurrent spontaneous pneumothorax, bullous emphysema and renal tumors. Malignant renal tumors are the most ominous internal manifestation linked with the syndrome. We present a case report of BHD that was diagnosed in a private practice. The origins of BHD, diagnosis, treatment and management are reviewed.

**Case Report**

A 75-year-old Caucasian male of English and Scottish descent presented to the dermatologist’s office for routine evaluation for skin cancer. Past medical history was significant for prostate cancer, diabetes mellitus, hypertension, hyperlipidemia, actinic keratoses and multiple basal cell and squamous cell carcinomas. During the course of examination, numerous firm, small, 2-4mm, skin-colored papules of the nose and nasolabial folds were noted (Figure 1). After biopsy showed these to be fibrofolliculomas (Figure 2), further questioning revealed a history of three spontaneous pneumothoraces as a young man in his 20s. Additionally, he admitted to having a brother with similar skin lesions on his face and a maternal grandfather that died due to “kidney issues” in his 60s. A clinical diagnosis of Birt-Hogg-Dubé syndrome was made, and consultation with a medical geneticist was arranged. Due to high out-of-pocket costs, he declined FLCN genetic testing, but he and his family members were informed of the dominant inheritance of the condition. A recommendation was given that all first-degree relatives (daughter and siblings) be managed as if they have BHD until proven otherwise. Thus far, screening exams of chest X-ray and renal ultrasound have been within normal limits for the patient.

**Histopathology**

Punch biopsy of a papule on the right cheek showed a proliferation of fibroblasts and collagen in the upper dermis. A portion of a distorted follicle is present at the edge of the lesion. Diagnosis: Fibrofolliculoma (Figure 2).

**Discussion**

Birt-Hogg-Dubé syndrome was first characterized in 1977.1 The initial report of this autosomal-dominant genodermatosis described 15 persons of a single Canadian family spread over three generations, all afflicted with numerous small, firm papules on the scalp, forehead, face and neck.1,3 Histological processing at the time diagnosed the lesions as fibrofolliculomas and trichodiscomas, while numerous acrochordons were also noted clinically. No mention was made of any internal association with pulmonary or kidney disorders.

Interestingly, two years previous in 1975, Hornstein and Knickenberg described a similar genodermatosis consisting of multiple perifollicular fibromas of the face, neck and trunk with associated intestinal polyyps.4 With time and further evolution of histological techniques, these entities are now considered to be the same syndrome – BHD syndrome.

Though intestinal polyyps have not been definitively linked to BHD, there are some important internal associations – namely, lung cysts, recurrent spontaneous pneumothorax, bullous emphysema and renal tumors.5-7 Though many other benign and malignant processes have been reported as occurring in BHD patients, no other associations have been proven.5

In 2001, BHD was shown to be caused by mutations in a gene encoding the folliculin protein (FLCN), which was mapped to chromosome 17p11.2-3.11 Folliculin appears to be highly conserved across species, is expressed normally in skin, kidneys and lungs and has been theorized to have a tumor-suppressor function affected through the mTOR pathway. Fifty-three unique germline mutations have been discovered in all but two exons of FLCN, with most occurring within a hypermutable hotspot in exon 11.11-12 Despite extensive testing, however, no specific genotype-phenotype correlations have been discovered.

Individuals with similar mutations can have markedly different disease expressions ranging from no clinical findings to the complete trifecta of skin, lung and renal disorders.

As in the defining case series first described decades ago, most patients with BHD have numerous small, skin-colored to whitish papules on the face, neck and trunk, with rarer oral papules reported as well.5,13 Usually, these lesions appear after the age of 20. Histologically, these growths, including many of the so-called trichodiscomas, perifollicular fibromas and acrochordons, are thought to be part of the same morphological spectrum of fibrofolliculomas. Concerning internal associations, the most ominous is that of renal cancer. Different studies reveal slightly different numbers, but most series indicate around 27% of BHD patients develop renal tumors at a mean age of approximately 50 years old.14,15 It should be noted, however, that a BHD patient as young as 20 years old has developed renal cancer.10 Typically, patients with BHD develop chromophobe and mixed-pattern chromophobe/oncocytic renal tumors, but other subtypes such as clear-cell can occur as well.9 Also of note, the renal cancer of BHD tends to be multifocal and bilateral in over half of patients, but there are surprisingly few reports of metastasis.14,15 Concerning the lungs, it has been shown that, though lung function is usually unaffected, over 80% of adult BHD patients have lung cysts, most often in the basilar areas.6 Again, numbers may vary slightly, but in one series the prevalence of pneumothorax in BHD patients was 24%.16

First and foremost, any diagnosis of BHD should prompt genetic counseling for the patient as well as first-degree relatives. FLCN gene testing should be offered, and first-degree relatives should be thoroughly screened for signs of the syndrome. Moving on to the specific stigma of the syndrome, fibrofolliculomas are obviously benign in nature but can have psychosocial impact, especially in younger patients. As such, they can be treated depending on the wishes of the patient. Laser ablation, shave and cautery, and curettage and hyfrecation have all been advocated by various authors. Skin tags and polypoid pendulous fibrofolliculomas can be excised in the usual manner. There are no established evidence-based guidelines for surveillance of renal cancer, but at least some authors consider annual MRI from the age of 20 years old to be best. According to consensus, ultrasound is insensitive for small tumors, while yearly CT would cause unacceptably high cumulative radiation doses.8,17,18 Concerning BHD patients and lung involvement, little intervention is needed other than imaging and pulmonary referral for at-risk patients such as pilots or deep-sea divers. Additional considerations include thoracic CT before any general anesthesia and discouragement of smoking.

**References**

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