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The medical field and the medical industry are in a state of never-ending change. We are disappointed that both Novartis Pharmaceuticals and 3M can no longer be sponsors of the JAOCD. Both of these companies have had major internal issues that will prevent them from their continued sponsorship of the JAOCD. Novartis and 3M have been friends and supporters of the AOCD and the JAOCD. As editors of the JAOCD, we thank them for giving freely, allowing us to bring the JAOCD to the level where we are today.

We also recognize the companies that have been and continue to be, our Founding Sponsors. Allergan Skin Care, with all of their innovative products, stepped up to the plate 4 years ago and have continued to support the JAOCD. Connetics Corporation, with their continuing unique line of foam-based topical medications, also was there from the beginning and continues to give their unrelenting support for this journal. Global Pathology Laboratory, providing national 24 hour expert dermatopathology evaluation, has always been there when we requested support. Medicis-The Dermatology Company, has been committed to the JAOCD from the beginning as a Founding Sponsor, providing the dermatology community with ongoing science and new and innovative products. We thank all of our Sponsors for their continued support and for their confidence in our efforts to provide dermatologists with a unique journal that has been created and designed specifically as a journal by and for residents in dermatology.

Stiefel Laboratory, committed to dermatology, has been a long time supporter of the AOCD. Recently Stiefel has made the decision to be a Sponsor of the JAOCD. Dorothy Germino at Stiefel Laboratories did not hesitate when asked to sponsor our journal. We welcome Stiefel to our family at the JAOCD and look forward to a long and mutually beneficial relationship.

We have outsourced the grammar and spelling proofing responsibility of the JAOCD to Julie Layton at Freelance Proofreading and Editing. Working with Julie has been easy and a pleasure. We are committed to improving the JAOCD in every way possible.

As a reminder to the AOCD residents in dermatology, the Education Evaluation Committee (EEC) has made it mandatory for each resident to submit their annual paper for publication to a medical journal. As the editors of the JAOCD, we hope that the residents will consider the JAOCD when the time comes for them to consider where they will submit their annual papers. It is a relatively easy process to submit a paper to the JAOCD. Simply go to www.aocd.org and click on the JAOCD icon at the bottom of the screen. It is our hope that every resident in the AOCD will be encouraged by their Program Directors to submit their annual and other papers to the JAOCD throughout their three years of residency program.

Again we extend our sincere appreciation for the continued support to our Founding Sponsors: Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services and Medicis-The Dermatology Company. We again welcome Stiefel Laboratory as a new sponsor of the JAOCD!

Jay S. Gottlieb, D.O., F.O.C.O.O. (Editor)
Stanley E. Skopit, D.O., F.A.O.C.D. (Editor)
James Q. Del Rosso, D.O., F.A.O.C.D. (Editor)
Safety Information:
LOPROX® Shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults. If no clinical improvement is shown after 4 weeks of treatment, the diagnosis should be reviewed. LOPROX Shampoo is contraindicated in individuals who have shown hypersensitivity to any of its components. The most common adverse reactions are pruritus, burning, erythema, seborrhea, and rash. If a reaction suggesting sensitivity or irritation should occur, treatment should be discontinued and appropriate therapy instituted. Avoid contact with eyes; if contact occurs, rinse thoroughly with water. Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years. There is no relevant clinical experience in patients who have a history of immunosuppression, who are immunocompromised, or who have diabetic neuropathy.

References:
Loprox® Shampoo (ciclopirox) 1%

Rx Only

FOR TOPICAL USE ONLY
NOT FOR OPHTHALMIC, ORAL OR INTRAVAGINAL USE
KEEP OUT OF REACH OF CHILDREN

DESCRIPTION

Loprox® (ciclopirox) Shampoo 1% contains the synthetic antifungal agent, ciclopirox. Each gram (equivalent to 0.96 mL) of Loprox Shampoo contains 10 mg ciclopirox in a shampoo base consisting of Purified Water USP, Sodium Laureth Sulfate, Disodium Laureth Sulfosuccinate, Sodium Chloride USP, and Laureth-2.

Loprox Shampoo is a colorless, translucent solution. The chemical name for ciclopirox is 6-cyclohexyl-1-hydroxy-4-methyl[1H]pyridone, with the empirical formula C_{20}H_{19}NO_4 and a molecular weight of 327.27. The CAS Registry Number is [29342-05-0]. The chemical structure is:

![Chemical Structure of Ciclopirox]

CLINICAL PHARMACOLOGY

Mechanism of Action

Ciclopirox is a hydroxypyridone antifungal agent although the relevance of this property for the in vivo activity of the drug is not known. Ciclopirox acts by chelation of polyvalent cations (Fe3+, Al3+), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell.

Pharmacokinetics and Pharmacodynamics

In a study in patients with seborrheic dermatitis of the scalp, application of 5 mL ciclopirox shampoo 1% twice weekly for 4 weeks, with an exposure time of 3 minutes per application, resulted in detectable serum concentrations of ciclopirox in 6 out of 18 patients. The serum concentrations measured throughout the dosing interval on Days 1 and 29 ranged from 10.3 ng/mL to 13.2 ng/mL. Total urinary excretion of ciclopirox was less than 0.5% of the administered dose.

INDICATIONS AND USAGE

Ciclopirox is fungicidal against Malassezia furfur (Pityrosporum spp.), P. ovale, and P. orbiculare. Ciclopirox acts by chelation of polyvalent cations (Fe3+ or Al3+), resulting in the inhibition of the metal-dependent enzymes that are responsible for the degradation of peroxides within the fungal cell. The clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

Clinical significance of antifungal activity in the treatment of seborrheic dermatitis is not known.

INDICATIONS AND USAGE

Loprox Shampoo is indicated for the topical treatment of seborrheic dermatitis of the scalp in adults.

CONTRAINDICATIONS

Loprox Shampoo is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS

Loprox Shampoo is not for ophthalmic, oral, or intravaginal use.

Keep out of reach of children.

PRECAUTIONS

General

If a reaction suggesting sensitivity or irritation should occur with the use of Loprox Shampoo, treatment should be discontinued and appropriate therapy instituted. Contact of Loprox Shampoo with the eyes should be avoided. If contact occurs, rinse thoroughly with water.

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

There is no relevant clinical experience with patients who have a history of immunsuppression (e.g., extensive, persistent, or unusual distribution of dermatomycoses, recent or recurring herpes zoster, or persistent herpes simplex), who are immunocompromised (e.g., HIV-infected patients and transplant patients), or who have a diabetic neuropathy.

Information for Patients

The patient should be instructed to:

1. Use Loprox Shampoo as directed by the physician. Avoid contact with the eyes and mucous membranes. If contact occurs, rinse thoroughly with water. Loprox Shampoo is for external use on the scalp only. Do not swallow.

2. Use the medication for seborrheic dermatitis for the full treatment time even though symptoms may have improved. Notify the physician if there is no improvement after 4 weeks.

3. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blisters, swelling, or oozing) indicative of possible allergic reaction.

4. Notify the physician if any disorder other than that for which it is prescribed.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of Loprox Shampoo or ciclopirox.

The following in vitro genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in the Ames Salmonella and E. coli assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells, with and without metabolic activation (positive); chromosome aberration assays in V79 Chinese hamster lung fibroblast cells in the presence of supplemental Fe3+, with and without metabolic activation (negative); gene mutation assays in the HPRT test with V79 Chinese hamster lung fibroblast cells (negative); and a primary DNA damage assay (i.e., unscheduled DNA synthesis assay in A549 human cells) (negative). An in vitro cell transformation assay in BALB/c 3T3 cells was negative for cell transformation. In an in vivo Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at a dosage of 5000 mg/kg body weight.

Ciclopirox olamine was administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats, rabbits, and monkeys, respectively. Histological examination of offspring at litter death (i.e., approximately 13, 42, 54 and 26 times the maximum recommended human dose based on body surface area comparisons, respectively) was not informative.

Dermal embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day/ciclopirox in rats and rabbits, respectively. At human equivalent doses of approximately 31 and 54 times the maximum recommended human dose based on body surface area comparisons, respectively, there were no adverse or well-controlled studies of topically applied ciclopirox in pregnant women.

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

Pregnancy

Teratogenic effects: Pregnancy Category B

Oral embryofetal developmental studies were conducted in mice, rats, rabbits and monkeys. Ciclopirox or ciclopirox olamine was orally administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 77, 125, 80 and 38.5 mg/kg/day ciclopirox in mice, rats and rabbits, respectively.

Oral embryofetal developmental studies were conducted in rats and rabbits with ciclopirox olamine dissolved in PEG 400. Ciclopirox olamine was topically administered during the period of organogenesis. No maternal toxicity, embryotoxicity or teratogenicity were noted at the highest doses of 92 mg/kg/day and 77 mg/kg/day/ciclopirox in rats and rabbits, respectively.

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There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women.

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

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Loprox Shampoo is administered to a nursing woman.

Pediatric Use

Seborrheic dermatitis may appear at puberty, however, no clinical studies have been done in patients younger than 16 years.

Geriatric Use

Pharmacokinetic and Pharmacodynamic data indicated no differences in systemic exposure between the elderly and younger subjects, but greater sensitivity to adverse effects in some older individuals cannot be ruled out.

ADVERSE REACTIONS

In 626 patients treated with Loprox Shampoo twice weekly in the two pivotal clinical studies, the most frequent adverse events were itching in 1% of patients, and application site reactions, such as burning and erythema, in 1% of patients. Other adverse events occurred in individual patients only.

Adverse events that led to early study medication termination in clinical trials occurred in 1.5% (26/1738) of patients treated with Loprox Shampoo and 2.0% (12/661) of patients treated with shampoo vehicle. The most common adverse events leading to termination of study medication in either group was seborrhea. In the Loprox Shampoo group, other adverse events included rash, pruritus, headache, ventricular tachycardia, and skin disorder. In the shampoo vehicle group, other adverse events included skin disorder and rash.

DOSAGE AND ADMINISTRATION

Wet hair and apply approximately 1 teaspoon (5 mL) of Loprox Shampoo to the scalp. Up to 2 teaspoons (10 mL) may be used for long hair. Lather and leave on hair and scalp for 3 minutes. A timer may be used. Avoid contact with eyes. Rinse off. Treatment should be repeated twice per week for 4 weeks, with a minimum of 3 days between applications.

If a patient with seborrheic dermatitis shows no clinical improvement after 4 weeks of treatment with Loprox Shampoo, the diagnosis should be reviewed.

HOW SUPPLIED

Loprox® (ciclopirox) Shampoo 1% is supplied in 120 mL plastic bottles (NDC 99207-010-10).

HOW SUPPLIED

Loprox® (ciclopirox) Shampoo 1% is supplied in 120 mL plastic bottles (NDC 99207-010-10). DISCARD unused product after initial treatment duration. Store between 15°C and 30°C (59°F and 86°F).

Manufactured for:

MEDICIS® Pharmaceutical Corp.
Scottsdale, AZ 85258

by: Pathene, Inc.

Mississauga, Ontario L5N 7K9

CANADA

PRESCRIBING INFORMATION AS OF FEBRUARY 2003
Dear fellow AOCD members,

It has been my pleasure representing you thus far this year. We have made a great deal of progress in many areas. One of my major goals has been to unify our members and reinforce the benefits of maintaining membership in our college. I have had excellent feedback regarding my solicitation of potential new members -- osteopathic dermatologists that for whatever reason have not realized the value of having or maintaining AOCD membership. With the growth of our training programs and the new or returning members, we may see our numbers increase dramatically in the next five years. These increasing numbers will allow us the assurance that our training programs maintain the high quality that we all want and expect. This will also allow us to consider other services for our members and maintain the excellent didactic sessions that we customize to our members' wants and needs.

Our coordinator for corporate development, Shirley Gottlieb, has been working diligently in her continuing attempt to maintain and attract corporate sponsors of our college. The funds that she acquires allow us to develop new educational opportunities for our residents, such as the Intendis dermatology mentoring grant. With this grant, the resident will have the opportunity to work with experts in our field and have the financial support of the AOCD.

As president, another of my personal areas of interest has been our residency training programs. We are constantly reviewing our programs and attempting to improve and address weaknesses. New programs are being developed to meet the demand for our specialty training and give our graduating osteopathic medical students an opportunity to achieve their goal of a career in dermatology. With the addition of new programs, it is our challenge to maintain the quality that we expect. As a program director myself, I constantly challenge myself and my co-trainers to improve the learning experience we offer our residents. Our residents have traveled to the finest programs in the country for elective rotations and have returned with exemplary evaluations. Their performances have enhanced our reputation in the greater world of dermatology. They present posters and or papers yearly at the AAD as well as at our AOCD meetings. They have been frequently published in international journals as well as our excellent JAOCD. I am proud of the osteopathic dermatologists that we have graduated from all of our programs. To honor our residents, I have developed a new award of academic excellence. This will be sponsored by the Medicis Corporation. The goal is to recognize the resident from each class that is deemed to be most worthy in regard to a set of criteria developed by our awards committee. I challenge all of our current residents to strive to achieve their greatest potential and take advantage of the unique opportunities that every program offers. The education evaluating committee endeavors to improve all of our programs and give every resident the opportunity to excel. We are open to any feedback you may have, both positive and negative.

Finally, I would like to publicly recognize the exemplary work done by our executive director, Becky Mansfield, and her husband, Rick, in maintaining the integrity of our AOCD office despite the illness of their daughter. We all hope and pray for a speedy recovery.
Uncombable Hair Syndrome: A Case Report

Scott A. Smith, D.O. *, Lisa N. Gelles, M.D. **
* 3rd year Dermatology Resident, University Hospitals of Cleveland, Case Western Reserve, Cleveland, Ohio
** Assistant Professor, Case Western Reserve University, MetroHealth Medical Center, Cleveland, Ohio

ABSTRACT

Uncombable hair syndrome is a rare hair shaft disorder that typically presents in the first year of life with hair that is light in color, coarse, wiry, stands away from the scalp, and is difficult to manage. Uncombable hair is diagnosed by scanning electron microscope, which on cross sectioning reveals triangular shaped hairs with longitudinal indentation, giving the hairs a reniform-to-heart shape. We are presenting an infant girl who presented at the age of 11 months with a 4-month history of a significant change in hair color and texture.

Case Presentation

An 11-month-old infant girl presented with a 4-month history of a change in color and texture of her hair. Per the patient's mother, her hair has gradually gotten lighter, kinkier, more difficult to comb, and seems to stand up on end. There has not been any noticeable increase in hair loss or breakage. The patient's growth and development have been normal. She has no significant past medical history and takes no medicines.

On examination, the infant is well developed, well nourished, and well appearing. Involved the entire scalp, there are coarse, blonde hairs that have a spangled appearance and stand away from the scalp. The patient's eyebrows, eyelashes, fingernails and toenails all appear normal. There are no dental abnormalities.

Figure 1 was taken of the patient at 2 years of age. The patient's sister began having comparable findings at the age of 10 months. The patient's great aunt had similar hair complaints as a child, which subsequently improved with age.

Light microscopy shows normal appearing hair shafts, without signs of abnormality. Scanning electron microscope on cross sectioning reveals triangular shaped hairs with longitudinal indentation, giving the hairs a reniform-to-heart shape. These findings are consistent with the diagnosis of uncombable hair syndrome.

Background

This disorder was first described in 1973 in the French literature by Dupré as “cheveux incoiffables”; that is, “uncombable hair,” and the same year described by Stroud as “spunglass” hair. The term pili trianguli et canaliculi was first used by Dupré and Bonafé in 1978. The monikers “uncombable hair” and “spunglass” come from characteristic clinical appearance. The disorder typically presents in the first year of life with hair that is light in color, coarse, wiry, stands away from the scalp, and is difficult to manage. The hair may have a glistening or spangled appearance secondary to the reflection of light off the surface of the irregularly shaped hairs. In most cases of uncombable hair syndrome, only the scalp hairs are affected and typically in a generalized distribution. A localized variant has been reported as well in a 5-year-old girl with involvement of her eyebrows, eyelashes, and scalp hairs.

Under scanning electron microscopy, these hairs have a canal-like groove running longitudinally along the length of the hair. The hairs may be reniform, heart shaped or triangular, thus the name pili trianguli et canaliculi. Salinas proposed that the name be changed to pili canaliculi in 1988. Camacho et al. had a patient with the Rapp-Hodgkin variant whose hair shafts had two longitudinal grooves, pili bicanaliculi, and had a quadrangular shape. Therefore, Camacho et al. also felt that the name pili canaliculi should be used, as pili trianguli et canaliculi was too limiting.

Etiology

It has been proposed that uncombable hair presents in both a sporadic and an inherited pattern. The inherited cases have been suggested to be autosomal dominant with variable penetrance and expression or autosomal recessive. The cause of the structural defect has yet to be elucidated. Stroud et al. proposed that premature keratinization caused an error in complementation of the inner root sheath. In 1987, Stone et al. reported a Japanese girl with uncombable hair syndrome, who on biopsy had one hair with asymmetrical atrophy of the hair bulb, suggesting that the defect of the matrix resulted in the characteristic longitudinal groove. Amino acid analysis, X-ray diffraction analysis, and stress-strain analysis showed no abnormalities compared to normal hair. However, the spun glass hair was shown to have decreased solubility in TUM buffer. The significance of this is unclear at this time.

Associated Disorders

Longitudinal grooves along the hair shaft, although characteristic of, are not exclusive to uncombable hair syndrome. Pili trianguli et canaliculi most commonly has no other associated somatic disorders. However, when another condition is present the most frequent one is ectodermal dysplasia including the Rapp-Hodgkin and the Witkop variants.
Other disorders that have been reported to be associated with longitudinal grooving include progeria, hypohidrotic ectodermal dysplasia, retinal dysplasia, crystalline cataract, digit abnormalities, dental abnormalities, phaIangoeiphipshe dysplasias, wooly hair nevi, ichthyosis vulgaris, Marie-Unna hypotrichosis, acquired progressive hair kinking, drug-induced kinking, uremia, pili torti, atopic dermatitis, progressive alopecia areata, hamartomas, nail abnormalities, lichen sclerosis, and monilethrix.18,19,20 Uncombable hair syndrome by itself is not associated with any physical, neurologic, mental or developmental abnormalities.19

Rest and Fretzin showed that the characteristic longitudinal grooves could also be found in normal volunteers, although less than 10% of the hairs were affected.21 Those with uncombable hair syndrome were shown to have involvement of at least 50% of their hairs.20,21,22

Treatment

There are four reported cases of successful treatment with the use of oral biotin.23,24,25 One of the patients was evaluated by scanning electron microscopy, and no changes in the hairs’ structural morphology were shown even though there was increased manageability of the hair.25 Manageability may be increased with hair length. Hair quality may improve with age, and spontaneous remission is not uncommon.

Discussion

This syndrome is rare disorder with a characteristic clinical presentation. It has been reported in both inherited and sporadic forms. Subjects are usually affected within the first year of life. The hair is characterized by bundles of hair arranged in all different directions that resist being brushed or combed. The hair is often a silvery-blond color with a spangled or glistening appearance. Uncombable hair syndrome by itself is not associated with any physical, neurologic, mental or developmental abnormalities.18 The diagnosis is made by scanning electron microscopy. Hair quality may improve with oral biotin, increased length, and with age (as with the proband’s great aunt).

References

ABSTRACT

Fabry disease (FD) is a rare, X-linked, recessive lysosomal storage disorder caused by a deficiency of the alpha-galactosidase A enzyme. This abnormality leads to an accumulation of neutral glycosphingolipids in the vascular endothelium and visceral tissues. Due to its inheritance pattern, males are more commonly affected than females. This case report presents a unique case of FD presenting itself in a heterozygous female carrier. In general, patients with FD have an increased risk of death from renal, cardiovascular, and cerebrovascular complications. By discussing the signs and symptoms, diagnostic testing, and novel treatment options, the dermatologist may be aided in the diagnosis and treatment of Fabry disease.

Case Report

A 57-year-old female presented with a five-year history of “blood blisters” located on her chest, abdomen, and proximal extremities. She reported intermittent, spontaneous bleeding of these lesions. The patient denied any associated pruritus, paresthesias, or tenderness. No symptoms of hemoptysis, hematuria, or melena were elicited. Her family history revealed similar skin lesions on her brother, who has since died in his fifties secondary to a cardiac cause. Physical examination demonstrated linear, violaceous petechiae and papules following the relaxed skin tension lines, as well as scattered papules on her torso (Fig 1). There were no lesions in the oral mucosa, distal extremities, or genital region. Ophthalmologic, cardiac, and renal exams revealed no abnormalities. Basic blood work was within normal limits. An alpha-galactosidase A enzyme level revealed a low normal level. The skin biopsy demonstrated ectatic, thin-walled vascular channels in the papillary dermis along with encased epidermal vascular spaces (Fig 2). The patient was subsequently diagnosed with Anderson-Fabry disease, also known as Fabry disease or angiokeratoma corporis diffusum.

Discussion

Fabry disease (FD) is a rare, X-linked, recessive disorder caused by a defect in the lysosomal enzyme, alpha-galactosidase A. This results in progressive deposition of neutral glycosphingolipids throughout the vascular endothelium and visceral tissues. While FD primarily affects males, heterozygous female carriers, with random X-chromosome inactivation, have been identified with varying degrees of disease expression.1

The clinical signs and symptoms of Fabry disease are heterogeneous and reflect the extent of enzyme activity, as well as the damage to involved organ systems. The eyes, skin, and kidneys, as well as the cardiovascular, cerebrovascular, and peripheral nervous systems are primarily affected.

Neuropathic pain and episodic “crises” or acroparesthesias are generally the earliest and most debilitating symptoms of Fabry disease. Fortunately, these symptoms improve over time. Roughly 70% of affected males and 10% of affected females have paraesthesias.12

The characteristic cutaneous manifestation of Fabry disease is diffuse angiokeratomas located in the “bathing trunk” distribution of approximately 70% of affected males and 30% of female carriers.1 These lesions present as small, dark-red to blue-black papules found in clusters with the propensity of becoming hyperkeratotic. Mucosal involvement is common. Angiokeratomas increase in size, number, and distribution over time. Hypohidrosis, and less commonly anhidrosis, can also occur, causing heat intolerance.2

The most common extracutaneous manifestation of Fabry disease is corneal opacities, which are short-like configurations found on slit-lamp examination. Most affected males and 70 to 80% of female carriers are affected.1 This finding is the most common presenting sign of Fabry disease in female carriers. Other ocular abnormalities include subcapsular cataracts and tortuous vascular lesions of the retina and conjunctiva.3

Renal involvement can progress from nonspecific polyuria to proteinuria,14 uremia, and eventually isothenuria if there is not early diagnosis and prompt treatment. Female carriers are usually asymptomatic, or have minimal symptoms, while 90% of affected males have proteinuria.1 Polarization microscopy of the urine reveals birefringent lipid globules often demonstrating the characteristic Maltese crosses.4

Cardiac manifestations of Fabry disease include but are not limited to angina, congestive heart failure, mitral valve insufficiency, cardiomyopathy, hypertension, and arrhythmias.14 While less than 1% of female carriers have cardiac symptoms, affected males can die prematurely from a myocard-
hyperkeratosis, and elongation of the rete epidermal changes including acanthosis, mainly in the papillary dermis with overlying Fordyce, solitary angiokeratoma, and angiokeratoma circumscriptum, angiokeratoma of Mibelli, angiokeratoma of including angiokeratoma of the diagnosis. Finally, angiokeratomas are classically found in five disease entities, the glomerular filtration rate may also assist in the early diagnosis of Fabry disease. Therefore, careful monitoring is crucial to prevent any secondary complications. In general, without a positive family history, Fabry disease has been a diagnostic challenge due to its varied clinical manifestations and the potential involvement of various organ systems. No distinct set of guidelines has been established thus far. Therefore, a multidisciplinary approach can assist in the early diagnosis of Fabry disease. In addition to a high index of suspicion through clinical signs and symptoms, urine polarization microscopy demonstrating lipid globules and Maltese crosses can contribute to a diagnosis of FD. Furthermore, plasma, peripheral leukocytes, or cultured skin fibroblasts revealing reduced or absent alpha-galactosidase A enzyme activity is helpful toward the diagnosis. However, in heterozygous females, the enzyme level may be near normal. Testing for alpha-galactosidase A enzyme gene mutations can confirm the diagnosis. Imaging studies including MRI of the brain to locate ischemic changes, echocardiogram to rule out cardiac abnormalities, and nuclear scan of the kidneys to evaluate the glomerular filtration rate may also assist in the diagnosis. Finally, angiokeratomas are classically found in five disease entities, including angiokeratoma of Mibelli, angiokeratoma circumscriptum, angiokeratoma of Fordyce, solitary angiokeratoma, and angiokeratoma corporis diffusum. A skin biopsy demonstrating numerous, dilated, thin-walled, congested capillaries located mainly in the papillary dermis with overlying epidermal changes including acanthosis, hyperkeratosis, and elongation of the rete ridges signifies the lesion to be specifically associated with angiokeratoma corporis diffusum or Fabry disease. Management of Fabry disease is multifaceted, ranging from symptomatic and palliative treatment to prevention of secondary complications. Most important, correcting the enzyme deficiency through enzyme-replacement therapy (ERT) is optimal. To prevent the relentless accumulation of glycosphingolipids, ERT is an option since the advent and approval of two recombinant enzyme preparations, agalsidase-alpha (Replagal®) and agalsidase-beta, (Fabrazyme®). Fabrazyme is the only form approved in the United States and is dosed at 1 mg/kg for intravenous administration. Warnock reports that the phase IV randomized, placebo-controlled study of ERT is promising, indicating that the incidence of renal, cardiovascular, and cerebrovascular events and death were decreased by 43% with agalsidase-alpha, at 1 mg/kg every two weeks as compared to the placebo group. However, it is controversial as to when to institute ERT. Desnick et al. recommends initiating therapy as soon as signs and symptoms first appear. Breunig and colleagues advocate for earlier intervention, prior to end-organ manifestations such as proteinuria and left ventricular hypertrophy. In either case, the benefits of ERT are undeniable, and ongoing studies will continue to shed more light on this promising treatment option. As discussed earlier, neuropathic pain is a major cause of morbidity that can be controlled with anticonvulsants including phenytoin, carbamazepine, and gabapentin. In addition, antiplatelet and anticoagulant therapy may be necessary for stroke prevention. With worsening proteinuria, angiotensin-converting enzyme inhibitor therapy should be implemented immediately to prevent further renal damage. Combination therapy with angiotensin-receptor blockers may be superior to either drug alone. If end-stage renal disease occurs, hemodialysis and/or renal transplantation are then required. Masson et al. comments on the importance of the transplant because of the renal protection imparted by its own α-galactosidase A enzyme, which fails to protect other organs. Research on gene therapy is on the horizon and may also aid in altering the natural history of this disease. Our patient, who is a heterozygous female carrier of Fabry disease, represents the minority of patients inflicted by this condition. She is doing well and returns for yearly exams to monitor disease progression. Periodically, symptomatic angiokeratomas are treated with electrodesiccation. The purpose of this case report is to present a unique case of Fabry disease in which an X-linked, recessive inherited condition presented itself in a female patient. Although uncommon, it is important to consider such a diagnosis in a female patient, when the signs and symptoms and a history of a similar familial presentation are demonstrated, in order to halt the progression of a potentially debilitating disease. Mild, late-onset disease may occur in heterozygous females as a result of uneven inactivation of the X chromosome that does not carry the mutation. By presenting the signs and symptoms, diagnostic testing procedures, and treatment options of Fabry disease, one may feel more comfortable diagnosing and treating this condition.

References
Treatment with Tacrolimus 0.1% Ointment in En Coup de Sabre: A Case Report

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ABSTRACT

En coup de sabre is a rare variant of linear scleroderma. It is characterized by ivory-colored to hyperpigmented, band-like, firm, sclerotic plaques predominantly involving the frontoparietal scalp and paramedial facial regions. These lesions can extend to involve underlying structures. Various topical, systemic, and surgical therapeutic modalities have been used in the past; however, none have been shown to be consistently effective. Moreover, some of these treatment modalities do carry significant risks. Herein we report a case of an 11-year-old male with en coup de sabre who responded to treatment with topical tacrolimus 0.1% ointment. Topical tacrolimus 0.1% ointment may be a safe treatment option for patients with en coup de sabre. However, further studies are needed to prove the long-term efficacy of this medication.

En coup de sabre is a rare variant of linear scleroderma. It is characterized by band-like, ivory-colored to hyperpigmented, firm, sclerotic patches and plaques preferentially occurring in the frontoparietal scalp and face in the paramedian regions. It almost always presents in a unilateral distribution; however, bilateral distributions have been reported. These atrophic patches and plaques can extend to involve underlying subcutis, muscle, and osseous structures resulting in obvious deformities and eventual cicatricial alopecia. Treatment modalities have overall been unsatisfactory. Various topical, systemic, ultraviolet, and surgical therapies have been used, but none have been shown to work consistently, and some of these treatment modalities can carry significant risks of potential adverse effects. Herein we report a case of an 11-year-old male with en coup de sabre who responded to treatment with topical tacrolimus 0.1% ointment.

Case Report

An 11-year-old, Caucasian male presented with a one-year history of two patches located on the forehead region. There was reported associated irritation, pruritus, and scaling. He had no other associated symptomatology. The patient’s mother reported that the onset occurred approximately one month after applying sunscreen. There was a question whether this could be due to underlying contact dermatitis. Self treatment with multiple over-the-counter emollients, scar gel and patches resulted in minimal improvement. The patient was seen and evaluated by primary care physician and was given topical terbinafine ointment for presumed dermatophytosis; however, patient had minimal response and lesions persisted. Patient was a healthy child with no significant past medical or surgical history. There was no family history of connective-tissue disorder or epilepsy.

On physical examination, patient had two firm, atrophic, hyperpigmented, slightly yellowish patches with no overlying scales. These linear, band-like patches were located on the right paramedian forehead, central forehead, and the glabellar region extending from the frontal hair line to the nasal dorsum, measuring 2.0 cm x 1.0 cm and 4.0 cm x 1.0 cm, respectively (Figure 1). A 4-mm punch biopsy was completed on the right upper forehead. Histologically, there was a sclerosing dermatitis with noted septal panniculitis (Figure 2-3). Overall, histologic features were consistent with linear scleroderma en coup de sabre. All laboratory studies were unremarkable, including complete blood count with differential, lyme titer, ANA on Hep2 substrate, anti-Scl70 and anti-centromere antibodies. Radiologic brain studies were not done.

The patient was initially treated with topical desonide 0.05% ointment twice daily and cefadroxil monohydrate 500 mg twice daily for one month with some improvement. Because of the possible adverse effects with long-term use of topical corticosteroids, the patient was switched to a non-steroidal alternative. Topical calcipotriene 0.005% ointment was prescribed; however, the patient’s insurance company did not cover the medication.

Figure 1
An 11 year old male with 2 slightly hyperpigmented atrophic band-like patches on the right forehead and glabellar region extending down to the nasal dorsum.
include retinal vascular anomalies, 13-14, ocular findings, although uncommon, are not usually part of the clinical presentation. Ophthalmologic and neurological abnormalities should be performed in en coup de sabre patients exhibiting neurological manifestations. However, the routine use of CT and MRI studies in clinically asymptomatic patients is still in question.

In addition to ocular and neurological findings, there have also been reports of associated dental abnormalities, malocclusion, and tongue changes. 27 Furthermore, there have been a few isolated case reports of rare association and coexistence of en coup de sabre with aortic regurgitation, hereditary deficiency of C2, systemic lupus erythematosus, and lichen planopilaris. 31 The diagnosis of en coup de sabre can be made on the basis of clinical presentation and confirmed with a skin biopsy including subcutis. Characteristic histologic features include thickening and sclerosis of reticular dermis and subcutis, superficial and deep perivascular lymphocytic infiltrate with plasma cells and occasional eosinophils that can extend downward to involve the dermal-subcutaneous and septal-lobular junctions, and the presence of atrophic eccrine glands. Furthermore, small blood vessels may develop thickened walls and lumen narrowing. 1, 32

The diagnosis of localized scleroderma including en coup de sabre can not be reliably confirmed by specific laboratory tests. However, it can be further supported by the presence of eosinophilia, hypergammaglobulinemia, and ANA. 33 These laboratory findings have been reported to be common in all forms of localized scleroderma. 1, 14 Blood eosinophilia and hypergammaglobulinemia with polyclonal elevation of serum IgG and IgM occurs in approximately 50 percent of patients with linear scleroderma and usually corresponds to those with clinically active disease and clinical progression. 1, 14 The presence of serum autoantibodies have also been reported in children with linear scleroderma. When present, the most commonly detected autoantibodies are ANA, anti-ssDNA, and rheumatoid factor. In addition, antihistone and anticientromere antibodies have been reported but were less common. 1, 14 Previous reports suggest that the presence of these serum autoantibodies may correlate with disease activity. 1, 14 However, it does not necessarily correlate with systemic disease. 9

The etiology and pathogenesis of en coup de sabre are unknown. Implicated causes include infection, namely borrelia burgdorferi, environmental factors, i.e. trauma, surgery, biological stress, vaccinations, and exogenous toxins, and autoimmune phenomenon. Previous reports have shown that some cases have presented along the lines of Blaschko, which suggests that the predisposition for en coup de sabre may begin during early embryogenesis secondary to underlying genetic cutaneous mosaicism. 24-27 Despite the many theories, the underlying etiology and pathogenesis of en coup de sabre remain to be elucidated.

Parry-Romberg syndrome is almost always considered in the differential diagnosis of en coup de sabre. Parry-Romberg syndrome is a rare, distinct variant of linear morphea. It is characterized by progressive facial hemiatrophy sclerosis and ocular changes including heterochromia, enophthalmos, and uveitis. 29-30 There is a considerable overlap with regard to features between Parry-Romberg syndrome and en coup de sabre, but the latter can be distinguished clinically by more prominent cutaneous sclerosis with associated hyperpigmentation and alopecia, while the
former typically has more extensive involvement of the lower face and minimal to no cutaneous sclerosis. Histologically, they can share similar features; however, patients with en coup de sable often have a more significant connective-tissue fibrosis, adnexal atrophy, and mononuclear infiltrate. The relationship between Parry-Romberg syndrome and en coup de sable remains unclear. Some authors believe that they are distinct entities, while others believe that they are overlapping conditions within the spectrum of the same disease process.1,2-4

The long-term prognosis of patients with en coup de sable and linear scleroderma is no different from the general population. However, they can be associated with a varying degree of morbidity, often necessitating treatment. Currently, there is no consistently effective treatment for en coup de sable. Treatments have been directed at immunosuppression and at measures correcting disease-related deformity. Various therapeutic modalities have been used, including topical therapies with corticosteroids, calcipotriene 0.005% ointment, and topical capsaicin; systemic therapies with corticosteroids, retinoids, vitamin E, vitamin D3 (oral calcitriol), penicillin, interferon gamma, and immunosuppressants i.e. hydroxychloroquine, methotrexate, salazopyrine, cyclosporine, cyclophosphamide, D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; and ultraviolet phototherapy, namely oral or D-penicillamine, and azathioprine; 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Impressive results.
Less irritation.

Whether used alone\textsuperscript{1,2} or with a retinoid,\textsuperscript{3} Duac\textsuperscript{®} Topical Gel provides proven efficacy with superior tolerability.

For topical BPO/antibiotic acne therapy,
Your Choice is Clear\textsuperscript{TM}

IMPORTANT SAFETY INFORMATION
Duac Topical Gel is indicated for the topical treatment of inflammatory acne.
Duac Topical Gel is contraindicated in patients who have shown hypersensitivity to any of its components or lincomycin, and in those with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and colitis have been reported with the use of topical clindamycin. Discontinuation is recommended if significant diarrhea develops.

Please see accompanying Brief Summary of Prescribing Information.
Duac® Topical Gel
(clindamycin, 1% - benzoyl peroxide, 5%)

For Dermatological Use Only.
Not for Ophthalmic Use.
Rx Only

INDICATIONS AND USAGE
Duac® Topical Gel is indicated for the topical treatment of inflammatory acne vulgaris.

Duac® Topical Gel has not been demonstrated to have any additional benefit when compared to benzoyl peroxide alone in the same vehicle when used for the treatment of non-inflammatory acne.

CONTRAINDICATIONS
Duac® Topical Gel is contraindicated in those individuals who have shown hypersensitivity to any of its components or to licorice. It is also contraindicated in those having a history of regional enteritis, ulcerative colitis, pseudomembranous colitis, or antibiotic-associated colitis.

WARNINGS
ORALLY AND PARENTERALLY ADMINISTERED CLINDAMYCIN HAS BEEN ASSOCIATED WITH SEVERE COLITIS WHICH MAY RESULT IN PATIENT DEATH. USE OF THE TOPICAL FORMULATION OF CLINDAMYCIN RESULTS IN ABSORPTION OF THE ANTIBIOTIC FROM THE SKIN SURFACE. DIARRHEA, BLOODY DIARRHEA, AND COLITIS (INCLUDING PSEUDOMEMBRANOUS COLITIS) HAVE BEEN REPORTED WITH THE USE OF TOPICAL AND SYSTEMIC CLINDAMYCIN. STUDIES INDICATE A TOXIN(S) PRODUCED BY CLOSTRIDIUM 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. ENDOSCOPIC EXAMINATION MAY REVEAL PSEUDOMEMBRANOUS COLITIS. STOOL CULTURE FOR CLOSTRIDIUM DIFFICILE AND STOOL ASSAY FOR CLOSTRIDIUM DIFFICILE TOXIN MAY BE HELPFUL DIAGNOSTICALLY. WHEN SIGNIFICANT DIARRHEA OCCURS, THE DRUG SHOULD BE DISCONTINUED.

Large bowel endoscopy should be considered to establish a definitive diagnosis in cases of severe diarrhea. Antiperistaltic agents such as opiates and diphenoxylate with atropine may prolong and worsen the condition. Diarrhea, colitis, and pseudomembranous colitis have been observed to begin up to one day after treatment. Proctoscopy may reveal pseudomembranes. If the condition persists, the patient should be referred to a gastroenterologist for further evaluation.

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against Clostridium difficile colitis.

PRECAUTIONS
General: For dermatological use only; not for ophthalmic use. Concomitant topical acne therapy should be used with caution because a possible cumulative irritancy effect may occur, especially with the use of peeling, desquamating, or abrasive agents.

The use of antibiotic agents may be associated with the overgrowth of nonsusceptible organisms, including fungi. If this occurs, discontinue use of this medication and take appropriate measures.

Avoid contact with eyes and mucous membranes.

Clindamycin and erythromycin containing products should not be used in combination. In vitro studies have shown antagonism between these two antimicrobials. The clinical significance of this in vitro antagonism is not known.

Information for Patients: Patients using Duac® Topical Gel should receive the following information and instructions:

1. Duac® Topical Gel is to be used as directed by the physician. It is for external use only. Avoid contact with eyes, and inside the nose, mouth, and all mucous membranes, as this product may be irritating.

2. This medication should not be used for any disorder other than that for which it was prescribed.

3. Patients should not use any other topical acne preparation unless otherwise directed by their physician.

4. Patients should report any signs of local adverse reactions to their physician.

5. Duac® Topical Gel may bleach hair or colored fabric.

6. Duac® Topical Gel can be stored at room temperature up to 25°C (77°F) for up to 2 months. Do not freeze. Keep tube tightly closed. Keep out of the reach of small children.

7. Before applying Duac® Topical Gel to affected areas, wash the skin gently, rinse with warm water, and pat dry.

8. Excessive or prolonged exposure to sunlight should be limited. To minimize exposure to sunlight, a hat or other clothing should be worn.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Benzyol peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzyol peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic Tg.AC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with Duac® Topical Gel. Clindamycin phosphate was not genotoxic in Salmonele typhimurium or in a rat micronuclear test. Benzyol peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonele typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells. Studies have not been performed with Duac® Topical Gel or benzyol peroxide to evaluate the effect on fertility. Fertility studies in rats treated orally with up to 300 mg/kg/day of clindamycin (approximately 120 times the amount of clindamycin in the highest recommended adult human dose of 1.5 g) or Duac® Topical Gel, based on mg/m², revealed no effects on fertility or mating ability.

Pregnancy: Teratogenic Effects: Pregnancy Category C: Animal reproduction studies have not been conducted with Duac® Topical Gel or benzoyl peroxide. It is also not known whether Duac® Topical Gel can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Duac® Topical Gel should be given to a pregnant woman only if clearly needed.

Developmental toxicity studies performed in rats and mice using oral doses of clindamycin up to 600 mg/kg/day (240 and 120 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) or subcutaneous doses of clindamycin up to 250 mg/kg/day (100 and 50 times the amount of clindamycin in the highest recommended adult human dose based on mg/m², respectively) revealed no evidence of teratogenicity.

Nursing Women: It is not known whether Duac® Topical Gel is secreted into human milk after topical application. However, orally 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.

Pediatric Use: Safety and effectiveness of this product in pediatric patients below the age of 12 have not been established.

ADVERSE REACTIONS
During clinical trials, all patients were graded for facial erythema, peeling, burning, and dryness on the following scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The percentage of patients that had symptoms present before treatment (at baseline) and during treatment were as follows:

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<tr>
<th>Local Reactions with Use of Duac Topical Gel</th>
<th>% of Patients Using Duac Topical Gel with Symptom Present</th>
<th>Combined Results from 5 Studies (n = 397)</th>
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<tr>
<td>Before Treatment (Baseline)</td>
<td>During Treatment</td>
<td>Before Treatment (Baseline)</td>
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<td>Erythema</td>
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<td>Dryness</td>
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(Percentages derived by # subjects with symptom score/# enrolled Duac subjects, n = 397).

HOW SUPPLIED
Duac® (clindamycin, 1% - benzoyl peroxide, 5%) Topical Gel is available in a 45 gram tube - NDC 0145-2371-05.

Prior to Dispensing: Store in a cold place, preferably in a refrigerator, between 2°C and 8°C (36°F and 46°F). Do not freeze.

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Keep tube tightly closed. Keep out of the reach of small children.

U.S. Patent Nos. 5,466,446, 5,446,028, 5,767,098, and 6,013,637

Patent Pending

Stiefel Laboratories, Inc.
Coral Gables, FL 33134

BRIEF SUMMARY OF PRESCRIBING INFORMATION

REFERENCES:

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ABSTRACT

Angiosarcoma, an uncommon and highly aggressive tumor, can present in an array of clinical forms. Diagnosis is based on histological findings and immunohistochemical markers but is complicated by the fact that classic histology may not always be present. Diagnostic delay remains a problem in treating angiosarcoma and contributes to its dismal prognosis. Treatment options include excision, radiation and chemotherapy. The clinician must possess a high index of suspicion and be aware of the variations in the clinical presentation of angiosarcoma.

Case Report

A 75-year-old white male presented in April 2005 with a complaint of bleeding from a violaceous, 5-mm papule over his right temple when he shaved over it. The lesion clinically resembled a traumatized venous lake and was removed via excision with electrodessication and submitted for pathological evaluation. The report showed a collection of histiocytes in the superficial dermis, inflammatory or reactive in nature.

Approximately two months later, the patient presented with an erythematous ecchymotic area looking almost traumatic in nature on his right temple, which the patient felt was a bruise because he was on Coumadin. By mid August the "bruise" was noted to have worsened, and new nodular areas had developed. Due to the patient’s age, the clinical presentation, and a high index of suspicion for cutaneous angiosarcoma, the area was surgically excised and submitted for pathological evaluation. The findings revealed a malignant mesenchymal neoplasm, which was most consistent with superficial malignant fibrous histiocytoma; however, there were some focal areas that stained positive for factor VIII, which could not completely rule out angiosarcoma. Clinically, the presentation was behaving like an angiosarcoma, and a consultation was made with an oncologist. A two-week follow-up visit revealed a recurrence along the midline incision as well as several new vascular lesions (Figure 1). Excisional biopsies were taken of all new areas, and the pathology revealed endothelial cells that stained positive for factor VIII. A definitive diagnosis of cutaneous angiosarcoma was made.

Of interest, two weeks following suture removal, several new areas of angiosarcoma had developed (Figure 2).

Due to the patient’s negative PET scan, the oncologist felt there was no role for adjuvant chemotherapy. The patient is currently undergoing radiation treatments.

Review of the Literature

Accounting for less than 1-2% of soft tissue neoplasms, angiosarcoma is a rare but highly aggressive tumor that can occur at any site, including visceral organs, breast and bone. However, the most common site affected is the skin. Classically, cutaneous angiosarcoma presents on the head and neck of elderly individuals with a male preponderance of 2:1. Head and neck angiosarcoma accounts for approximately 50% of cutaneous angiosarcoma cases. Most occur in Caucasian individuals, although there have been reports in Afro-Americans and Asians. Cutaneous angiosarcoma can also develop in the presence of chronic lymphedema (Stewart-Treves Syndrome) and post-irradiation. The majority of angiosarcoma cases arising in the presence of chronic lymphedema are secondary to mastectomy and constitute 10-20% of cutaneous cases of angiosarcoma. Post-irradiation angiosar-
Angiosarcoma is uncommon and occurs in women who have undergone subsequent radiation therapy after breast-sparing surgery with lymphadenectomy. In addition to chronic lymphedema and irradiation-induced angiosarcoma, environmental toxins such as vinyl chloride, thorotrast and arsenic have been linked to angiosarcoma. There has also been some suggestion that actinic damage and trauma might play a role in causing angiosarcoma, but there is no direct evidence to support this.

The exact etiology of cutaneous angiosarcoma remains unclear. While there is a general agreement that angiosarcoma is of endothelial origin, it has not been determined if there is a malignant change in existing endothelial cells or if an endothelial malignant change occurs in pluripotential mesenchymal cells. Furthermore, the focus of the controversy lies in whether the primary malignant change is of vascular or lymphatic derivation. Evidence in favor of a vascular origin include CD31 (platelet-endothelial cell adhesion molecule type I) expression, presence of blood in vascular channels, and factor VIII-related antigen. The ability of vascular endothelial-derived growth factor (VEGF) to produce well-differentiated angiosarcoma in a murine model also favors a vascular origin. Conversely, the presence of discontinuous basal lamina and absence of dendritic peri-
cytes lend support to a possible lymphatic origin. Mentzel et al argued in favor of a lymphatic origin, pointing out that only 14% of cutaneous angiosarcomas stain positively for CD34 (human hematopoietic progenitor cell antigen).

The controversy surrounding the etiology of angiosarcoma has resulted in the usage of varying terms to describe the disease. In 1926, Livingston and Klemperer offered the first description of the clinical and histopathological characteristics of angiosarcoma. Almost 40 years later, in 1964, E.W. Jones distinguished scalp angiosarcoma as its own entity and coined the term "malignant angioendothelioma." Several other documented cases of angiosarcoma surfaced in between these two events and were categorized as hemangiosarcoma, hemangioendothelioma, and lymphangiosarcoma. While there appears to be an issue of semantics regarding a correct description, Knight et al asserts that angiosarcoma be used to collectively refer to this tumor. The fact that well-differentiated cutaneous angiosarcoma of the head and neck cannot be histologically distinguished from lymphangiosarcoma or angioendothelioma gives credence to the usage of angiosarcoma as an encompassing term.

Not only does the aggressive nature of angiosarcoma offer a clinical challenge, but so does its variation in clinical presentation. Though the head and neck are the most documented locations, angiosarcoma can arise anywhere on the skin, including the plantar aspect of the foot, as documented in a case report by Wolf and Pasquino. Angiosarcoma can present with a variety of features, which often causes delay in diagnosis and subsequent treatment. The most "classic" presentation of angiosarcoma is asymptomatic, bluish plaque at the head and scalp of elderly men. Bruising may also be associated with a suspected traumatic event or use of anticoagulant or antiplatelet therapy. Angiosarcoma can also present as nodules with or without ulceration or possess features that mimic an infectious process. Cases of angiosarcoma have also been documented as chronic edematous plaques, recurrent angiodema, angioneurotic edema, and scarring alopecia. Other unusual presentations include rosacea-like clinical characteristics, such as an erythematous infiltrate or a rhinophyma-like appearance of the nose, and yellowish plaques above the eyelid resembling xanthelasmas and causing ptosis. Chapa et al also reported a case of well-differentiated angiosarcoma arising in a seroma of a post-craniotomy patient, and there has been a documented case of sclerodermic telangiectasia transforming into angiosarcoma.

While clinical manifestations may vary, it does appear that there is a correlation between clinical presentation and histopathological findings. Ecchymotic-like macules or plaques corresponded to well-to-moderately differentiated angiosarcoma, while nodular lesions were consistent with poorly differentiated tumors. Due to its spectrum of clinical presentation, the differential diagnosis of cutaneous angiosarcoma is great and dependent on the specific clinical variant presented. For instance, pigmented nodular lesions might suggest melanoma, or edematous plaques could also be a presenting sign of sarcoidosis, lymphoma, or granuloma faciale. Other potential diagnoses include Kaposi's sarcoma, hemangiomas, lupus pernio, dermatomyositis, and fixed drug eruptions. The vast array of possible differentials makes histological diagnosis imperative, but the histopathologic findings in angiosarcoma can vary depending on the degree of differentiation. In well-differentiated tumors, diagnosis relies upon the presence of irregular, anastomosing vascular channels that dissect through the dermis. These channels are lined by atypical endothelial neoplastic cells which may demonstrate hyperchromatism and pleomorphism. Some endothelial cells may even protrude into the vascular lumen and form papillations. Poorly differentiated tumors may display ill-defined vascular spaces with a proliferation of endothelial cells that show marked mitotic activity and take on a polygonal or spindle-cell shape. Consequently, the diagnosis of these tumors can be quite challenging and mistaken for carcinoma, melanoma or high-grade fibrosarcoma. The presence of cytotoxoplastic vacuoles within neoplastic cells helps to distinguish poorly differentiated angiogenous sarcoma from other potential diagnoses. Moreover, reticulin staining can aid in identifying vascular channels. In addition to vascular abnormalities, some angiosarcomas are associated with lymphedema and possess lymphangiomatous characteristics with an absence of erythrocytes in irregular vascular channels. There may also be a lymphocytic infiltrate surrounding the tumor as well as destruction of adnexal structures. Other histological variants of angiosarcoma have been documented, including granular cell angiosarcoma, where an eosinophilic infiltrate dominates the majority of cells found in the tumor, and angiosarcoma with foamy cells. Immunohistochemical stains, such as CD31, CD34, factor VIII-related antigen, and Ulex europaeus I lectin can be helpful in diagnosing angiosarcoma. CD34 and factor VIII-related antigen help identify angiosarcoma but also stain positive in non-vascular tumors. CD31 stain offers an advantage in that it is the most sensitive and specific of the immunohistochemical markers for endothelial tissue. However, the problem remains that the immunohistochemical markers are negative in many cases of angiosarcoma and are therefore unreliable as a sole means of diagnosis.

Since angiosarcoma typically has diffuse, ill-defined margins and tends to have multifocal involvement, treatment is difficult and recurrence is common. Metastasis occurs via hematogenous or lymphatic spread with the most common site being the lymph nodes followed by the lungs, liver, and bone. Treatment modalities include wide excision, radiation, chemotherapy or a combination thereof. Surgery is typically reserved for smaller, focal lesions usually less than 5 cm in diameter, but a cure is often unattainable since the tumor has a tendency to spread beyond clinical margins. There has been a case of Mohs chemosurgical microscopic technique used to successfully treat angiosarcoma. Radiation is an effective treatment, especially when used post-surgically, and may also be beneficial to control subclinical disease. Chemotherapeutic agents have shown mixed success in treating angiosarcoma. Doxorubicin used in combination with other agents and paclitaxel are among the most promising drugs. Spieh et al reported therapeutic efficacy of interferon alpha-2a and 13-cis-retinoic acid. Because angiosarcoma is an endothelially derived tumor, there is also some speculation that
utilizing antiangiogenic therapies, such as thalidomide, could be effective in the treatment of angiosarcoma.\textsuperscript{2,20}

In spite of treatment, the prognosis for angiosarcoma is poor, with a five-year survival rate estimated at 10-35%.\textsuperscript{2} Holden et al reported a five-year survival rate of 12%, with a median time of survival of 15 months.\textsuperscript{3} Complete surgical excision and tumor size serve as two significant factors influencing prognosis.\textsuperscript{4} Maddox and Evans noted that a tumor size of < 5 cm was associated with a favorable prognosis.\textsuperscript{24} A study performed by Holden et al supported this, demonstrating that tumors < 10 cm in diameter had a significantly increased chance of survival than larger tumors.\textsuperscript{5} Other prognostic indicators, such as sex, age of the patient, and clinical appearance, were not statistically significant in affecting prognostic outcome.\textsuperscript{24} Moreover, histological differentiation appears to offer little prognostic value.\textsuperscript{3} Interestingly, the presence of a lymphocytic infiltrate and a lack of appendageal involvement are associated with a better prognosis.\textsuperscript{25} There is also some suggestion that low mitotic counts favor a better prognosis.\textsuperscript{4,25} Despite these positive prognostic factors, angiosarcoma remains a therapeutic challenge and has a high mortality rate.

Angiosarcoma is both a diagnostic and a therapeutic challenge for clinicians. We must be aware of the varying presentations of angiosarcoma and possess a high index of suspicion in order to make an accurate and opportune diagnosis. Concurrently, we must also face the poor prognosis associated with angiosarcoma and investigate the available and appropriate treatment options for our patients while hoping for more therapeutic advances in the near future.

References
An 85-year-old man presented to our office with a four-month history of slowly enlarging lesions on his left temple and left arm. He also complained of asymptomatic “lumps” at the base of the right neck. The patient's past dermatologic history was positive for multiple actinic keratoses and a basal cell carcinoma. He missed his last dermatology visit and had not been evaluated for greater than six months. His pertinent medical history revealed an electively, non-treated form of invasive prostate cancer, which was diagnosed twelve months prior to his presentation to the dermatology office. Because of the patient's age and his multiple health issues, he declined any aggressive treatment. He agreed only to palliative care. Upon presentation, the patient was primarily concerned about his skin lesions, as they had increased in size and became more symptomatic.

Figure 1 A
Violaceous to red-brown subcutaneous nodules on the left temple

Figure 1 B
Close-up view: Violaceous to red-brown subcutaneous nodules on the left temple

Figure 1 C
Violaceous to red-brown subcutaneous nodule on the left arm

Figure 1 D
Bound-down skin with underlying coalescent, subcutaneous nodules

Histopathology:
Three 3-mm punch biopsies were performed to the two temporal and one left extremity nodule. A hematoxylin-eosin (H&E) stained section of the medial temporal lesion at 10X magnification revealed extensive replacement of the dermis by anastomosing cords and aggregates of neoplastic epithelial cells (Fig 2 A). The same section at 40X and 63X magnification illustrated neoplastic cells with eosinophilic cytoplasm and large, hyperchromatic nuclei (Fig 2 B). Neoplastic cells with extensive mitotic figures were noted to be attempting to form glandular structures and extensive mitotic figures were noted (Fig 2 C). Several immunohistochemical stains were performed, including leukocyte common antigen, Melan A, S100 protein, Keratin, Prostate Specific Antigen (PSA), and Prostatic Acid Phosphatase (PAP). PSA at 40X (Fig 3 A) and PAP at 63X magnification (Fig 3 B) illustrated diffuse and strong
positive staining, confirming the diagnosis of metastatic prostate adenocarcinoma.

Discussion:

Prostate adenocarcinoma is the second most common type of cancer in men, second only to adenocarcinoma of the lung. There are 200,000 new cases of prostate cancer diagnosed each year, and 30,000 of these patients die of the disease. It is estimated that 10% of cancer-related deaths in men in the United States are secondary to prostate cancer. Prostate cancer most frequently metastasizes to bone, liver, lungs, and adrenal glands, but rarely to the skin. Cutaneous lesions are an extremely rare finding in invasive prostate cancer, accounting for less than 0.5% of all metastatic cases. This is notable when compared to a 5% cutaneous metastasis rate from most other internal malignancies. There have been approximately 70 cases of cutaneous metastasis from prostate cancer reported in the literature. Subcutaneous metastatic lesions appear to be even more uncommon, with less than 50 cases reported.

The characteristic, relatively non-specific lesions of metastatic prostate adenocarcinoma are multiple, asymptomatic, violaceous to red-brown papules or nodules. The most common cutaneous sites include the lower abdomen, genitals, groin, anterior thighs, nipples, periaureolar skin, and head. Lesions of metastatic adenocarcinoma of the prostate described in the literature have mimicked trichoepitheliomas, pyoderma gangrenosum, erysipeloides, cylindromas, morphea, acanthosis nigricans, and angiosarcoma. The diagnosis of cutaneous metastasis from prostate cancer is a grave finding. The majority of patients die within six months of this diagnosis. Cutaneous metastasis is therefore associated with advanced disease and no therapy is described as being curative. Several treatments including hormonal therapy, chemotherapy, androgen blockade, and local radiation therapy have been reported as satisfying for slowing progression of metastatic disease, as well as aiding in relief of uncomfortable symptoms. The patient in our care was prepared for the diagnosis of cutaneous metastases from his prostate cancer. He did not want further therapy, and followed up with his oncologist for palliative care. It should be stressed that metastatic prostate cancer should be included in the differential diagnosis in any elderly male presenting with enlarging or unusual cutaneous or subcutaneous lesions.

References:

Inflammatory Linear Verrucous Epidermal Nevus (ILVEN): A case report and review of the literature

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ABSTRACT

Appearing as a series of linear, scaly patches and papules, Inflammatory Linear Verrucous Epidermal Nevus (ILVEN) is most often observed in female pediatric patients. Complete epidemiology of this condition has yet to be clearly elucidated. ILVEN usually clears by adolescence but may occasionally remain into adulthood. This paper describes a case of ILVEN with exacerbation of symptoms in association with pregnancy along with a review of the literature regarding this condition. We also provide a tear-out, easy-to-duplicate section of frequently asked questions as a patient education sheet that would be useful for patients and the parents of affected children.

Case Report

A pregnant 29-year-old female at 34 weeks of gestation presented with a slightly erythematous, serpiginous lesion on the posterior portion of her left thigh that had been present since approximately one year of age. She noted that the lesion had become thicken, more irritated, and more pruritic in the past few months (Figure 1). Physical exam revealed that the lesion was palpable with a verrucous character. At the time of presentation she gave a history of topical treatment of the lesion with topical steroids of varying potency.

Histopathologic Findings

A 4mm-punch biopsy was performed and regular alteration of parakeratotic areas of agranulosis and slightly depressed cup-like, areas of orthokeratotic hyperkeratosis with a distinct granular layer were appreciated (Figure 2a,b). Elongations of the rete ridges are also noted. These characteristic findings confirmed a suspicion of Inflammatory Linear Verrucous Epidermal Nevus (ILVEN).

Inflammatory Linear Verrucous Epidermal Nevus

ILVEN, a skin disease of childhood. It is usually seen in children less than five years of age, and for unknown reasons is more observed in female patients. Appearing as a series of verrucous, linear, scaly patches and papules, ILVEN may appear erythematous to brown in color. The most common sites of involvement include the arm, trunk, and leg. Complete and concise epidemiology of ILVEN has yet to be elucidated. ILVEN usually clears by adulthood but may occasionally remain into adulthood.

Figure 1
Inflammatory verrucous epidermal nevus. A slightly erythematous, serpiginous plaque with a verrucous surface on the posterior of left thigh.

Treatment

Because the vast majority of ILVEN treatments have been presented as case reports, there are no side-by-side comparison studies to illustrate which treatment modality is most effective. In the dermatological community it is well known that treatment of ILVEN is often very challenging; only anecdotal therapeutic effectiveness has been described. Additionally, most ILVEN treatments are currently used to provide relief of the symptoms that accompany ILVEN as opposed to complete cure of the condition.

Traditional therapies for ILVEN include cryotherapy, dermabrasion, electrofulguration, and chemical peels with trichloroacetic acid or phenol. These treatments however have fallen out of favor in recent years as they are uncomfortable, leave the patient with scarring, and often result in incomplete resolution of the lesion with recurrence as a common late finding.

Many dermatologists contend that excision of the affected site yields the highest success and surgical removal has proven to be effective in some cases. This is of course with limitations, including potential for scarring and increased potential for adverse effects that come with surgery. A surgical approach is obviously impractical if the lesion is extensive or located in an anatomical site where procedures can be difficult to perform.

Laser therapy has been recently used in the form of pulsed dye laser and carbon dioxide. Superpulsed carbon dioxide laser was first used in 2001 in a French study with satisfactory cosmetic result with no recurrence at two-year follow-up. In a recent study from Turkey in 2004, ILVEN was successfully treated with carbon dioxide laser. In this case, all symptoms associated to ILVEN resolved including redness, excoriations, scarring and itching. The only notable side effect was a pale discoloration limited to the treatment site.

A number of topical medications have been used to treat ILVEN: Calcipotriol oint-
ILVEN-RELATED QUESTIONS FREQUENTLY ASKED BY PARENTS

Q: WHAT IS ILVEN?
A: Very simply put, Inflammatory Linear Verrucous Epidermal Nevus (ILVEN) is a rare type of mole. These moles are due to an overgrowth of the upper layers of the skin (the epidermis).

Q: WHAT DOES ILVEN LOOK LIKE?
A: ILVEN is a scaly, reddish, bumpy growth on the skin that may be very itchy. As the name suggests, it usually presents linearly, as in “like a line”. It is almost always limited to one side of the body, usually on an arm or leg. For reasons unknown, the left leg is more often affected than the right.

Q: WHO GETS ILVEN?
A: ILVEN is most often a condition of childhood. 75% of people that get ILVEN are under 5 years old. Girls are affected four times more often than boys. Rarely, ILVEN may appear during adulthood. The exact cause of the condition is unknown.

Q: WHAT CAUSES ILVEN?
A: Although familial cases have been described, ILVEN usually arises spontaneously.

Q: HOW IS IT DIAGNOSED?
A: ILVEN may be diagnosed clinically, but a skin biopsy may be performed to confirm the diagnosis and rule out other conditions.

Q: WILL ILVEN SPREAD?
A: ILVEN may increase in size after its initial presentation. It usually does not move to other parts of the body.

Q: WHAT ARE THE SIDE EFFECTS OF ILVEN?
A: Intense itching is the most common complaint of patients who suffer from ILVEN. Parents and patients also report concerns regarding cosmetic appearance. Rarely, arthritis, or joint pain, may be associated. It is important to recognize this early and have it treated appropriately.

Q: CAN ILVEN BE CURED?
A: The good news is that ILVEN usually goes away on its own by adulthood. Unfortunately the fact that no one therapy has been consistently successful in the permanent resolution of ILVEN. Laser therapy, electrofulguration, liquid nitrogen cryotherapy, dermabrasion, and chemical peels are all methods that have been used to treat ILVEN. In most cases however, only the superficial portions of the lesions are removed. Surgical excision offers better success in regard to symptomatic relief but it may result in scarring.

Q: CAN ILVEN BE TREATED?
A: Treatments for ILVEN are usually not very effective. Different topical creams, such as prescription-strength topical steroids or calcipotriol may be helpful. Combination therapy with topical Tretinoin and Fluorouracil cream may have beneficial results, but long-term success requires continued use. (see “Treatment”)

Q: WHERE CAN I FIND OUT MORE INFORMATION ON ILVEN
A: www.ILVEN.org

References:

Other References:

Figure 2 (a,b)
Elongated rete ridges with alteration of parakeratotic areas of granulosus and slightly depressed, cup-like areas of orthokeratotic hyperkeratosis with a distinct granular layer.
Collision Tumor: A Case Report

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Abstract

Collision tumors are defined as two or more benign or malignant neoplasms arising in a single lesion. This case report describes a collision tumor of a melanoma with a seborrheic keratosis. The clinical, dermoscopic, and histological features of this lesion are described below. Collision tumors with a malignant component can be difficult to diagnose, secondary to certain features suggesting a benign neoplasm. Biopsies are recommended for lesions with unusual clinical and dermoscopic features.

History and Clinical Findings

A 76-year-old woman presented with a 5-mm by 7-mm papule on the back (Figure 1). The lesion was asymmetric with ill-defined borders and the colors of light brown, dark brown, and black. The left half of the lesion was smooth, whereas the right half had a crusted, scaly surface.

Dermoscopic Findings

Dermoscopic examination revealed a melanocytic lesion with a heterogenic pattern, biaxial asymmetry, three colors, and overall disorganization (Figure 2). There were comedone-like openings within the lesion, short lines at the periphery, and a moth-eaten border. There were also gray areas noted. This was an unusual pattern, and an excisional biopsy was performed.

Histopathological Findings

The global view of the biopsy specimen on low power demonstrates two distinct lesions (Figure 3). The left side of the biopsy specimen (Figure 4) at 10X magnification illustrates an increased number of solitary melanocytes asymmetrically along the dermal-epidermal junction with evident nuclear hyperchromatism and pleomorphism. There is exocytosis of melanocytes throughout the epidermis. Large, atypical melanocytes are located in the papillary dermis forming nests, cords, and strands. The right side of the biopsy specimen (Figure 5) at 10X magnification illustrates acanthosis with hyperorthokeratosis and horn pseudocysts.

Diagnosis

The diagnosis is a collision tumor of a melanoma and a seborrheic keratosis.

Discussion

The definition of a collision tumor is two or more benign or malignant neoplasms arising in a single lesion. In the article by Cascajo et al., only two of 54 collision tumors involved a seborrheic keratosis and a melanoma. Dermoscopic evaluation of the lesion pointed to features of a solar lentigo or seborrheic keratosis, but several characteristics suggested consideration of a malignant neoplasm. The benign features included short lines running together at the periphery and a moth-eaten border, which are generally noted in solar lentigines. The comedone-like openings are a finding of seborrheic keratoses. The malignant features included biaxial asymmetry, disorganization of the lesion, and gray areas suggesting regression.
Conclusion

Cutaneous collision tumors are extremely difficult to diagnose even with the help of dermoscopy. Biopsies are recommended for lesions with unusual clinical and dermoscopic features.

References

Epidermal Nevus Syndrome: A Case Report and Review of the Literature
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ABSTRACT

Epidermal nevus syndrome is a relatively rare neurocutaneous disorder that highlights the need for dermatologists to approach patients with a “holistic” manner and not focus solely on a patient’s cutaneous disease. In this paper, we will present an 11-year-old female whose systemic involvement required the expertise of multiple medical specialists to improve her quality of life. We will review both the cutaneous and systemic findings in patients with epidermal nevus syndrome and discuss the complex treatment options available.

Case Report

An 11-year-old African-American female presented to the Dermatology Clinic with a chief complaint of “skin lesions.” According to her mother, these multiple lesions had been present since birth and were gradually increasing in size. The patient’s past medical history was positive for autism, seizure disorder, and amytalplasia. The patient was taking oxcarbazepine. The patient’s past medical history was only significant for a skin biopsy at a nearby university dermatology clinic. The patient had no drug allergies. The family history was negative for similar lesions and there was no family history of neurologic disorders.

Physical examination revealed a healthy appearing 11-year-old African-American female with multiple hyperpigmented verruciform nevi on the neck, face, and lower lip. There were verruciform nevi involving the left gingival-buccal sulcus as well as the soft palate. The cutaneous and oral lesions only involved the right side of the body and a portion of the forehead. The forehead lesion did cross the midline. There was mild strabismus of her left eye. There were no vascular malformations, lipomas, or hemangiomas. The musculoskeletal exam did not reveal any significant abnormalities.

According to the patient’s mother, the cutaneous epidermal nevi were relatively asymptomatic. The patient complained of mild dysphagia to while eating solid food. The patient subsequently underwent indirect laryngoscopy and esophagoscopy, which revealed no evidence of laryngeal or esophageal pathology. Carbon dioxide laser ablation of the intraoral nevi was then performed under general anesthesia with complete resolution of the patients’ dysphagia. Her parents considered carbon dioxide laser treatment for her cutaneous lesions. She continued to have regular neurology, ophthalmology, otolaryngology, and dermatology evaluations.

Classification of Clinical Manifestations

Epidermal nevus syndrome (ENS) is a poorly defined entity that includes multiple organ systems. Associated disorders most often include bone, central nervous system, ocular, renal, vascular, and biochemical abnormalities. In addition, multiple types of nevi have been described in this syndrome. Nevi associated with the syndrome include: sebaceous nevus, nevus comedonicus, pigmented hairy epidermal nevus (Becker nevus), and the flat, velvety, nonorganoid nevus seen in Proteus syndrome.

These epidermal nevi are hamartomatous lesions originating from mutations of pluripotent epidermal cells during early embryonic development. Therefore, they tend to follow Blaschko’s lines, and the associated abnormalities often present on the ipsilateral side of the body. The complex and varied non-cutaneous abnormalities seen in these syndromes are due to genetic mosaicism in the mesodermal embryonal derivatives. The majority of cases are likely due to spontaneous mutations; however, patients classified as having Proteus and CHILD syndromes are found to have a predominant and X-linked inheritance respectively.

Schimmelpenning first described the association of linear epidermal nevi and CNS disorders in 1957. In 1975, Solomon and Esterly proposed a classification scheme grouping many different variants of nevi and systemic abnormalities under the term “epidermal nevus syndrome.” With the newer genetic testing techniques, these syndromes are now shown to represent six distinct subtypes of epidermal nevus syndrome, each with distinguishing clinical and genetic features. These include: sebaceous nevus syndrome, nevus comedonicus syndrome, Becker nevus syndrome, Phacomatosis pigmentokeratotica, Proteus syndrome, and congenital hemidysplasia with ichthyosiform nevus and limb defects (CHILD) syndrome.

In addition, in a recent review by Ruiz-Maldonado et al., a seventh category of “keratinocytic nevus syndrome” is proposed.

Management

Understanding that congenital nevi may be associated with multiple diverse and severe somatic abnormalities is the first step in managing the care of these children. Mucosal examination may reveal intraoral or ano-genital involvement. After a thorough cutaneous exam has been performed, cardiac, CNS, skeletal, and renal systems must be investigated. Nevi involving the head, neck and spinal area are indications for neurology consultation, as well as CT or MRI imaging. Children with CNS
involvement often exhibit seizure activity early in life.

Removal of congenital epidermal nevi needs to be individualized. Biopsy of changing lesions to rule out malignancy is always indicated. Tumors affecting vital structures may also require removal, i.e. oral, mucosal, and ocular lesions. Superficial epidermal nevi may be removed with a Q-switched ruby laser, CO2 Laser, or electrodessication. However, involvement of the epidermal appendages may necessitate more invasive removal techniques.

Summary

Children with epidermal nevus syndrome present a diagnostic and therapeutic challenge to the dermatologist. Like most genodermatoses, our understanding of the molecular and genetic basis of this diverse group of disorders has allowed for more accurate classification of patients. This syndrome requires the dermatologist to work closely with many different colleges to maximize the appropriate treatment of these children. Often, the dermatologist will be called upon to make the initial diagnosis. Therefore, it behooves us to provide our patients, their families, and our colleagues with an accurate diagnosis that will guide the future treatment plan for these children.

References
Introduction

Vasculitis is the inflammation and necrosis of blood vessel walls that presents with a wide range of clinical manifestations. The disease can range in severity from a self-limited, single-organ disorder to a life-threatening disease with the prospect of multiple-organ failure. The challenge is to not only recognize vasculitis, but also provide a specific diagnosis and treat the underlying etiologic condition.

Clinically, there is a broad range of cutaneous manifestations. Lesions may appear as petechiae or as erythematous-to-violaceous patches on the lower extremities. They may progress upward on the body and become palpable purpura or urticarial-like plaques. Erosions, ulcerations and necrosis may develop if left untreated.

Although the causes are diverse, there are limited histopathologic manifestations of vasculitis. A necrotizing vasculitis manifests as segmental areas of transmural infiltration and disruption of the vessel architecture by neutrophils with fibrinoid necrosis, and it is termed leukocytoclastic vasculitis (LCV). Endothelial swelling, granulocyte debris (leukocytoclasia), and extravasated erythrocytes are also commonly seen, but are not required for the diagnosis (Figure 1). The biopsy of any type of vasculitis is both site and time dependent. In lesions earlier than 12 hours or greater than 48 hours of age, a largely lymphocytic infiltrate can be seen. Some conditions are characterized by a solely lymphocytic vasculitis. This article will only discuss vasculitic conditions that have specific dermatologic signs secondary to vessel inflammation and small- and medium-vessel vascularites.

Classification

There continues to be confusion regarding the use of classification criteria, definitions, and diagnostic criteria. This is due to multiple factors, including paucity of knowledge regarding etiologies and overlapping clinical features. Several criteria have been used to classify vasculitis. These criteria include vessel size, severity of disease (cutaneous versus systemic), clinical signs and symptoms, histopathologic features, and primary or secondary disease. The earliest classification was based on vessel size and is still the most widely used. The American College of Rheumatology criteria of 1990 includes clinical, histologic, and disease history. The Chapel Hill Consensus Conference convened in 1992 and developed criteria for vasculitis based solely on histopathology. When approaching a patient in dermatology, we often focus on acute causes such as hypersensitivity or infection and chronic causes such as malignancy, collagen vascular disease, or cryoglobulinemia.

Common Etiologies of Cutaneous Vasculitis:

Current data shows that cutaneous vasculitis is associated with numerous conditions such as idiopathic (45-55%), infection (15-20%), inflammatory disease (15-20%), drug intake (10-15%), and malignancy (<5%).

Infection

Infections can cause lesions that mimic vasculitis as well as directly cause septic vasculitis. Infection occurs via any route, triggers an immune complex formation, the organism proliferates in a vessel wall, and vasculitis occurs. Occlusion of vessels causes necrosis. Bacteria, viruses, parasites, and fungi can all cause vasculitis, but not all can be discussed in the scope of this article.

The hepatitis B virus is estimated to cause 5% to 7% of polyarteritis nodosa cases. A known cause of cryoglobulinemic vasculitis includes infections, the vast majority represented by the hepatitis C virus (HCV). Up to 54% of patients with HCV have cryoglobulinemia. HIV infection is also associated with cryoglobulinemia and leads to vasculitis.

Several uncommon infections may cause vasculitis and should be noted. Ecthyma gangrenosum can be caused by pseudomonas, aeromonas, e.coli, candida, or aspergillus and is a known cause of necrotizing vasculitis in immunocompromised and neutropenic patients. Mycobacterium induces nodular vasculitis. Erythema induratum is a specific form of vasculitis associated with M. tuberculosis. Disseminated gonorrhea triggers thrombi formation, occlusion of vessels, and subsequent septic vasculitis. Other infections include chlamydia, rickettsial pox, Rocky Mountain spotted fever, and lepromatous leprosy. Aspergillosis is associated with IV catheter-site infection leading to vasculitis.
Inflammatory Disorders

Vasculitis can be associated with a broad range of inflammatory disorders including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren’s syndrome (SS), Behcet’s disease, and inflammatory bowel disease. Rheumatoid vasculitis affects 5% - 15% of patients with RA and is associated with increased morbidity and mortality. The most common presentation includes purpuric lesions, but palpable purpura, petechiae, digital infarcts, ulcers, nodules, livedo reticularis, and papulonecrotic lesions may also be seen (Figure 2).

Vascular injury in SLE can be a result of atherosclerotic, thrombotic, or inflammatory processes. Small arterioles and venules of the skin are the most commonly affected. Vasculitis occurs in association with a flare of the disease and has a poor prognosis. Vasculitis in SS commonly affects the skin and CNS. It affects 20% to 30% of patients, usually presenting as palpable purpura, urticaria, or ecchymosis of lower extremities. Symptoms are more frequent and severe in patients with associated cryoglobulinemia or positive SSA/SSB antigens. One form of SS is termed hypergammaglobulinemia of Waldenstrom. These patients are usually young females with recurrent leg petechial hemorrhages, polyclonal hypergammaglobulinemia, and HCV infection.

Vasculitis can be seen in patients with localized or systemic scleroderma. Smaller vessels are primarily involved, causing ulceration and scarring of fingertips and toes. Treatment is warranted in cases of infarctions, dermatologic lesions, neuropathy or organ failure. Treatment includes oral corticosteroids for mild disease and cyclophosphamide, azathioprine, or oral contraceptives, phenothiazines, allopurinol, thiazides, retinoids, and anti-influenza vaccines. Newer drugs have been implicated as well, including Interferon (IFN) and leukotriene inhibitors. Vitamins and nutritional supplements have been reported to cause LCV. Among illicit drugs, sympathomimetics are most commonly implicated. Chemicals such as insecticides and foods such as milk and gluten have induced vasculitis.

Drug-induced vasculitis is a diagnosis of exclusion, as there are no diagnostic laboratory studies. Eosinophilia is common in systemic drug-induced vasculitis (79%), but is only seen in 22% of skin-limited disease. To establish causality, a temporal relation of drug intake to eruption and effect of drug withdrawal and rechallenge should be noted.

Malignancy

Malignancy causes cutaneous vasculitis in 2% to 5% of cases. Paraproteinemina or a lymphoproliferative disorder most often induces vasculitis. A classic association exists between PAN and hairy cell leukemia. Vasculitis associated with solid tumors resolves with removal of the malignancy.

Small-vessel Vasculitis:

Cutaneous Small-vessel Vasculitis

Several causes of vasculitis are categorized by vessel size. An entity termed cutaneous small-vessel vasculitis (CSVV) is characterized by crops of lesions that resolve spontaneously in several weeks. Only small vessels are affected, thus lesions consist of purpura, papules, vesicles, and urticarial plaques. Lesions occur in dependent areas or at sites of trauma. Treatment is to remove any offending agent or to treat the underlying disease. Anecdotal therapy with colchicine has cleared several patients.

Cryoglobulinemic Vasculitis (CV)

A cryoglobulin is a monoclonal or polyclonal immunoglobulin that precipitates in cold. Type I consists of monoclonal IgM and is always associated with a malignant hematologic disorder such as multiple myeloma. Type II is a monoclonal IgM directed against IgG. Type III consists of polyclonal IgM against IgG. Types II and III are mixed cryoglobulins (MC). Cryoglobulins lead to vasculitis through inflammation of vessel walls by deposition of IgM-IgG complexes and complement activation. Type I disease is often associated with ischemic vasculopathy from direct obstruction of vessels by cryoglobulins.

Known causes of CV include infection, autoimmune disease, and lymphoproliferative disorders. The most common clinical manifestations of CV are purpura, arthralgias, or arthritis. Peripheral neuropathy and nephritic or nephrotic syndromes are also commonly seen. Palpable purpura of the lower extremities are the clinical hallmark of CV, with cold enhancing these lesions. The face and trunk are generally spared. Type I CV is associated with mucosal involvement, livedoid vasculitis, gangrene, Raynaud’s phenomenon, and cold-induced acrocyanosis. MC patients typically have purpuric or urticarial lesions.

Many serologic abnormalities exist in CV. Serum cryoglobulin levels do not correlate with disease severity. Hypocomplementemia may be found in up to 90% of patients, and C4 levels are low. Rheumatoid factor is positive in more than 70% of patients, and antinuclear antibody is positive in 20% of patients. Type II exhibits a monoclonal spike on serum electrophoresis.

Short-term corticosteroid treatment is sometimes effective for the purpura and arthralgias. For severe disease, IV corticosteroids may be used, but they do not affect the course of the disease. Steroids may be used in combination with cytotoxic agents and Interferon.

Urticarial Vasculitis

Approximately 5% to 10% of patients who present with chronic urticaria have urticarial vasculitis. Urticarial vasculitis is differentiated from urticaria by the duration of lesions longer than 24 hours, the presence of purpura and post-inflammatory pigmentation, and symptoms of burning. The lesions favor the trunk and proximal extremities and may last for up to three years.

Urticarial vasculitis is seen in 32% of patients with SS and 20% of SLE patients. Less common etiologies include infection (HCV), drug ingestion, and IgM or IgG gammopathies. Schnitzler’s syndrome is urticarial vasculitis associated with monoclonal IgM, fever, arthralgia, bone pain, and hepatomegaly. Other forms of urticarial vasculitis are defined by complement levels.

Laboratory evaluation may reveal high ESR, hypocomplementemia, positive ANA, and hematuria. There are no randomized trials of treatments for urticarial vasculitis, and no effective therapy currently exists.

Henoch-Schonlein Purpura

Henoch-Schonlein purpura (HSP) is defined by the tetrad of palpable purpura, arthritis, GI involvement, and nephritis. It is associated with IgA immune complexes in the circulation and vessel walls. HSP is the most common systemic vasculitis in children. The disease usually follows an upper respiratory infection and takes an acute course. Cutaneous manifestations begin as symmetric macular erythema or urticaria and eventually manifest as purpuric, inflammatory petechiae (Figure 3). The lower extremities are commonly involved, and there is regression in 10 to 14 days. Renal involvement is associated with the spread of purpura above the waist with fever and an elevated ESR. In the absence of GI and renal involvement, the treatment of HSP is supportive.
Medium-vessel Vasculitis:

Polyarteritis Nodosa

Classic PAN is a multisystem disorder that often presents with a range of systemic signs and symptoms. It affects men more than women and can occur at any age. The patient presents with fever, weight loss, arthralgias, and malaise. It is estimated that approximately 5% to 7% of cases are due to HBV infection. The most common cutaneous sign is palpable purpura and occurs in approximately 20% to 50% of patients. Signs of medium-vessel vasculitis are common, including livedo reticularis, punched-out ulcers, and subcutaneous nodules. Patients are treated with corticosteroids, which improve the five-year survival.14

Cutaneous PAN is limited to the skin and occurs in 10% of PAN cases. It is the most common form of PAN in children. Cutaneous lesions are painful dermal nodules, usually located on the lower extremities near malleoli. These nodules may ulcerate, creating a “starburst” pattern of livedo reticularis. Lesions may heal with atrophic scars of atrophie blanche. This form of PAN is associated with streptococcal infection, inflammatory disease, or malignancy. Laboratory findings are similar to Wegener’s.14

Combined Small- and Medium-sized Vessel Vasculitis:

Wegener’s Granulomatosis

Wegener’s consists of a triad of necrotizing granulomatous inflammation of the upper and lower airways, systemic necrotizing small-vessel vasculitis, and pauci-immune glomerulonephritis. The majority of cases occurs in Caucasians and equally affects males and females. The skin is involved in up to 66% of cases and may be the presenting symptom. Palpable purpura is the most common, followed by ulcers. Papulonecrotic lesions, subcutaneous nodules, and ulcers are also found. Ulcers resemble those of pyoderma gangrenosum. Typical laboratory findings include elevated ESR and C-reactive protein, anemia, leukocytosis, and positive RF.15

Churg-Strauss Syndrome

Churg-Strauss syndrome courses through three distinct phases. The first phase is characterized by allergic rhinitis, nasal polyps, and asthma. The second phase consists of eosinophilic pneumonia, gastroenteritis, and peripheral eosinophilia. The final stage is systemic vasculitis with granulomatous inflammation, which may occur up to 30 years after initial presentation.16 Palpable purpura is seen in nearly half of all patients. Subcutaneous nodules, urticaria, and papulonecrotic lesions occur frequently. Laboratory findings are similar to Wegener’s.17

Physical Examination

Physical examination helps to identify both the size of vessel involvement and a specific diagnosis. Palpable purpura, pinpoint papules, vesicles, petechiae, splinter hemorrhages, pustules, and urticaria are indicative of small-vessel vasculitis. Subcutaneous nodules, livedo reticularis, ulcers, papulonecrotic lesions, and digital infarcts indicate medium-sized vessel involvement.

Laboratory Evaluation

Patients with suspected vasculitis should have the following studies: complete blood count, blood/urea nitrogen and creatinine, liver functions, urinalysis, stool guaiac, HBV/HCV serology, cryoglobulins, complement levels (C4, C3), and RF. If connective-tissue disease is suspected, an ANA is warranted. If symptoms of malignancy are present, a work-up to find the primary site should be done.

Treatment

The first step is to rule out any obvious infection, inflammatory disease, or malignancy. Any offending medications should be discontinued. Underlying diseases must be treated in an attempt to eliminate the vasculitis.
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Pityriasis Versicolor During Infancy

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ABSTRACT

Pityriasis versicolor is a dermatophyte infection that rarely afflicts infants. Here we report two unrelated infants who were affected with tinea versicolor infection on the forehead and the trunk.

Introduction

Pityriasis versicolor is a common superficial cutaneous infection caused by Malassezia furfur, a hyphal form of Pityrosporum orbiculare. The disease is more prevalent in tropical areas and most commonly seen in young adults.1 It is rarely reported under the age of one year.2,3,4 Malassezia furfur is part of the normal flora of the skin where it exists in a yeast phase. It has been found that 97% of clinically normal people may carry the yeast on the scalp and 92% on the trunk.5,6 The oval form was more common on the scalp (Pityrosporum ovale), whereas the spherical form was more common on the trunk (Pityrosporum orbiculare). The incidence of Malassezia furfur on clinically normal skin from the back of newborn infants and those aged six months, one year, five years, 10 years and 15 years was investigated by Faergemann and Fredriksson.7 In their study, they failed to demonstrate Malassezia furfur in children less than one year old and found the highest prevalence (93%) was in the 15-year-old children. On the contrary, in other reports, Malassezia furfur was isolated from the normal skin of 47% of 150 1-to-5-day-old infants8 and 37% of 15-year-old children.9 The pathogenesis of pityriasis versicolor is not clearly defined, but it is postulated that under certain circumstances, the normal skin organism converts from the yeast to the mycelial phase, leading to pityriasis versicolor. Factors that were suggested to precipitate the condition include: persistence of maternal androgen during the first few months of life,10 prematurity and hospitalization in neonatal intensive care units,2 high humidity and excessive sweating,11 close contact with an affected parent,1 systemic corticosteroid therapy,5 Cushing’s syndrome,12 immunosuppression associated with transplantation but not with AIDS, and physiological changes in skin lipids during puberty enhancing the fungal pathogenicity.13 Other predisposing factors that have been suggested are genetic, pregnancy and malnutrition, but evidence for these is not conclusive. Clinically, pityriasis versicolor presents as asymptomatic, scaly hypo- or hyperpigmented macular lesions that mainly occur on the upper trunk and arms. The macules frequently coalesce, producing patches of varying shapes and sizes. These pigmentary changes are thought to be due to the inhibition of melanin formation by substances, such as azelaic acid, produced by the enzyme activity of the yeasts.1 Examination of lesions under Wood’s light reveals a golden yellow fluorescence, and it is easily diagnosed by microscopic examination of skin scales mounted in 20% KOH to demonstrate the yeast and hyphal forms of Malassezia furfur. Culture is not helpful because Malassezia furfur is part of the normal skin flora. The differential diagnosis of pityriasis versicolor should include vitiligo, seborrheic dermatitis, and pinta. Pityriasis versicolor can be treated effectively with 2.5% selenium sulphide suspension or topical imidazole creams or ketoconazole shampoo. It should be noted that since Malassezia furfur is part of the normal flora of the skin, relapses frequently occur.1 Our two cases clearly demonstrate the importance of considering the diagnosis of pityriasis versicolor in infants presenting with pigmentary changes and the need for screening of affected family members so the condition could be treated effectively.

Discussion

Pityriasis versicolor is a chronic, mild and usually asymptomatic infection of the stratum corneum caused by the lipophilic yeast, Malassezia furfur. The disease is more prevalent in tropical areas. It can occur at any age but is most commonly seen in young adults and is comparatively rare in children, with an almost equal sex distribution.11 It is rarely reported under the age of one year.2,3,4 Malassezia furfur is part of the normal flora of the skin where it exists in a yeast phase. It has been found that 97% of clinically normal people may carry the yeast on the scalp and 92% on the trunk.5,6 The oval form was more common on the scalp (Pityrosporum ovale), whereas the spherical form was more common on the trunk (Pityrosporum orbiculare). The incidence of Malassezia furfur on clinically normal skin from the back of newborn infants and those aged six months, one year, five years, 10 years and 15 years was investigated by Faergemann and Fredriksson.7 In their study, they failed to demonstrate Malassezia furfur in children less than one year old and found the highest prevalence (93%) was in the 15-year-old children. On the contrary, in other reports, Malassezia furfur was isolated from the normal skin of 47% of 150 1-to-5-day-old infants8 and 37% of 15-year-old children.9 The pathogenesis of pityriasis versicolor is not clearly defined, but it is postulated that under certain circumstances, the normal skin organism converts from the yeast to the mycelial phase, leading to pityriasis versicolor. Factors that were suggested to precipitate the condition include: persistence of maternal androgen during the first few months of life,10 prematurity and hospitalization in neonatal intensive care units,2 high humidity and excessive sweating,11 close contact with an affected parent,1 systemic corticosteroid therapy,5 Cushing’s syndrome,12 immunosuppression associated with transplantation but not with AIDS, and physiological changes in skin lipids during puberty enhancing the fungal pathogenicity.13 Other predisposing factors that have been suggested are genetic, pregnancy and malnutrition, but evidence for these is not conclusive. Clinically, pityriasis versicolor presents as asymptomatic, scaly hypo- or hyperpigmented macular lesions that mainly occur on the upper trunk and arms. The macules frequently coalesce, producing patches of varying shapes and sizes. These pigmentary changes are thought to be due to the inhibition of melanin formation by substances, such as azelaic acid, produced by the enzyme activity of the yeasts.1 Examination of lesions under Wood’s light reveals a golden yellow fluorescence, and it is easily diagnosed by microscopic examination of skin scales mounted in 20% KOH to demonstrate the yeast and hyphal forms of Malassezia furfur. Culture is not helpful because Malassezia furfur is part of the normal skin flora. The differential diagnosis of pityriasis versicolor should include vitiligo, seborrheic dermatitis, and pinta. Pityriasis versicolor can be treated effectively with 2.5% selenium sulphide suspension or topical imidazole creams or ketoconazole shampoo. It should be noted that since Malassezia furfur is part of the normal flora of the skin, relapses frequently occur.1 Our two cases clearly demonstrate the importance of considering the diagnosis of pityriasis versicolor in infants presenting with pigmentary changes and the need for screening of affected family members so the condition could be treated effectively.

References:


Darier’s Disease

A 47-year-old man presents with multiple, greasy, crusted papules over his neck, chest, arms and shoulders (Figure 1). There was a negative family history for similar skin lesions. The patient admitted to suffering with Darier’s disease since adolescence. A skin biopsy was performed, which was diagnosed as Darier’s disease. The patient was prescribed a topical retinoid that cleared his skin lesions.

There are two types of Darier’s disease, Type I and Type II. Type I segmental develops from new mutations occurring in an otherwise healthy embryo. Type II segmental originates in a heterozygous embryo from post zygotic loss of the corresponding normal allele. This results in a clone that is either homozygous or hemizygous for the mutation. Others have described a variant called localized Darier’s disease histologically, however clinically there are no mucosal or nail changes. In addition, this variant has no familial history, and some would prefer to use the term “acantholytic dyskeratosis epidermal nevus.”

Darier’s disease is an autosomal-dominant genodermatosis with high penetrance but variable expression. Abnormal keratinization rarely skips a generation but may be so mild as to go unnoticed. The gene is localized to the 2-p region on the chromosome 12q23-24.1.1,2,4 This chromosome encodes a sarco/endoplasmic reticulum calcium ATPase pump (SERCA 2).4 Other diseases caused by a defect of the calcium ATPases include Hailey-Hailey and Brody’s disease (a rare musculoskeletal wasting disease).2

Darier’s-White disease, or keratosis follicularis, was first described independently by Darier and White in 1889.2 It is a rare disease characterized by loss of intercellular adhesion and disordered keratinization.3 Dermatologic skin changes manifest between the ages of six and 20 years old and are often misdiagnosed as seborrheic dermatitis or acne until topical agents, sun, heat, stress or sweating aggravates the lesions.2,3,4 Incidence in men and women are about equal. Peak incidence occurs between 11 and 15 years of age.2 Severity is unpredictable and fluctuates.4 There have been reports of peri-menstrual exacerbation of this disease.5 Typically, lesions appear on the central trunk, the supraclavicular fossa, the sides of the neck, the forehead, the ears and the scalp.6

Characteristic features include greasy, hyperkeratotic, firm papules that range in color from flesh to brown.2 Up to 80% of patients experience pruritus, which may be intractable.4,5 Pain is unusual. Patients may also experience eczematization (inflammation).4,5 Discrete papules found in flexures may coalesce into plaques and may become exophytic, malodorous and difficult to control.4 Rarely, the patient may experience skin fragility with painful erosions and fissuring. Greater than 95% of patients have acral involvement. Secondary skin infection is a common complication. Staphylococcus aureus and viral infection (both herpes and varicella viruses) may occur. V-shaped notching of the free edge of the nail with longitudinal red and white sandwich streaks are pathognomonic nail manifestations of Darier’s disease (Figure 2). Other nail manifestations include subungual hyperkeratosis and splinter hemorrhages.1,5 In addition, patients may have pits or punctuate keratotic papules on the palms and soles.1 Keratotic papules, indistinguishable from plane warts, are a sign of disease in infancy.3 Acrokeratosis verruciformis-like lesions on the dorsal aspect of the hands and feet is also an early sign of Darier’s disease.5

Oral lesions range from fine granular to coarse ‘pebbly’ appearance of the palate. Fifteen to 50% of Darier’s disease patients may have oral lesions, which are asymptomatic and require no treatment.2 There have been case reports of vulvar manifestations and parotid swelling.4

Darier’s disease has been associated with neuropsychiatric disorders including bipolar affective disorder, mental retardation, schizophrenia and epilepsy. Studies indicate, however, that Darier’s patients experience less psychological distress than atopic patients. Most problems stem from symptoms and feelings, while social relationships were relatively unaffected.3

Histologically, Darier’s disease has a loss of cohesion between suprabasal epidermal
cells (acantholysis). This results in suprabasilar clefting with papillomatosis and dyskeratosis with abnormal keratinocytes (corps ronds). There is hyperkeratosis with some degree of parakeratosis. Electron microscopy shows loss of the desmosomal protein attachments that normally link keratinocytes and periluclear aggregation of keratin filaments.

Treatment should be initiated with simple life changes. Irritation, the most common symptom, is best treated with simple emollients, containing urea and lactic acid, as soap substitutes. Keeping the skin cool by wearing cotton clothing will improve symptoms of irritation. Topical steroids are helpful for some patients. Sunblock should be used in patients with a history of photoaggravation. Lithium carbonate has been reported to cause exacerbations and if tolerated may result in flattening of the papules in the mild generalized or linear disease. Retinoids should be started every other day, then every day as tolerated. Alternating days of topical corticosteroid will help alleviate the erythema and pruritis.

Extensive disease may require oral retinoids, including etretinate, acitretin and isotretinoin. Ninety percent of patients with hyperkeratosis respond to oral retinoids. Although effective, these medications cause severe irritation, pruritus, drying and soreness of mucosal membranes. Triglycerides and cholesterol may be elevated, and abnormal renal function was reported. All oral retinoids should be discontinued during pregnancy. Isotretinoin is preferred over etretinate or acitretin in women of childbearing age because its effects are negligible at one month post-treatment instead of three years. Once on the oral retinoid, 70% of patients respond within one month. Studies indicate that isotretinoin should be started at 0.5 mg/kg/day and then adjusted accordingly. Initial treatment with acitretin is 10-25 mg/day and etretinate 30 mg/day.

Fluourouracil inhibits DNA synthesis, resulting in cell death, and therefore is effective in the hyperproliferative state of Darier’s Disease, yet no trials have been performed. Treatment response is two weeks. Calcipotriol in early studies indicated it was an extreme irritant and in some patients worsened their disease.

Secondary infections may manifest with exudates and painful blisters. Management is the standard of care for whatever the infectious agent is.

Surgery is the last resort in the treatment for hypertrophic skin lesions. Surgical procedures are often used in conjunction with medical treatment. Surgical approaches include electrocautery, dermabrasion, sharp debridement, split-thickness skin grafting, surgical excision and laser ablation. Dermabrasion has been reported to last as long as two and one-fifth years. Carbon-dioxide laser (Er:Yag) treatment has been shown to be successful for up to two years. Surprisingly, sufficiently deep (papillary dermis ablation) surgical intervention does not seem to cause scarring, as might be expected from the isomorphic phenomenon seen in response to trauma.

One study demonstrated that 13 of 16 patients with Darier’s disease that were treated with oral essential fatty acids improved after six to nine months.

In conclusion, Darier’s disease is a rare, autosomal-dominant genodermatosis affecting people between six and 20 years old. First described by Darier and White in 1889, it is characterized by loss of intercellular adhesion and disordered keratinization. Cutaneous lesions manifest as greasy, hyperkeratotic, firm papules that range in color from flesh to brown. Secondary infection with Staphylococcus aureus and viral infection may occur. Pathognomonic nail changes include V-shaped notching of the free edge of the nail with longitudinal red and white sandwich streaks. Treatment should start with simple life changes and progress to both oral and topical retinoids depending on the severity of the disease. Surgery should be last resort in treating this disease process.

Finally, DARDIS is a support group started in the UK. Further information may be obtained from the British Association of Dermatologists (www.bad.org.uk/about).
BOTOX® Cosmetic is indicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in patients 18 to 65 years of age.

Important Safety Information: BOTOX® Cosmetic is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any ingredient in the formulation. There have been rare reports of adverse events involving the cardiovascular system. Serious and/or immediate hypersensitivity reactions have been reported rarely. These reactions include anaphylaxis, urticaria, soft-tissue edema, and dyspnea.

The most common adverse events following injection include blepharoptosis and nausea. Less frequently occurring (<3%) adverse reactions include facial pain, erythema at the injection site, paresthesia, and muscle weakness. Patients with neuromuscular disorders such as ALS, myasthenia gravis, or Lambert-Eaton syndrome may be at increased risk of serious adverse events.

Please see brief summary of full prescribing information on following page.
BOTOX® COSMETIC (Botulinum Toxin Type A) Purified Neurotoxin Complex

INDICATIONS AND USAGE

BOTOX® COSMETIC is contraindicated for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients aged 40 years or older.

CONTRAINDICATIONS

BOTOX® COSMETIC is contraindicated in the presence of infection at the proposed injection site and in individuals with known hypersensitivity to any ingredient in the formulation.

WARNINGS

BOTOX® and BOTOX® COSMETIC contain the same active ingredient in the same formulation. Therefore, use of BOTOX® also has the potential to be associated with the use of BOTOX® COSMETIC. Risks resulting from administration at higher doses are not known.

Hypersensitivity Reactions

Some of the hypersensitivity reactions reported rarely have been serious. These reactions include anaphylaxis, urticaria, soft tissue edema, and dyspnea. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent and, consequently, the reactions cannot be reliably determined. If such a reaction occurs further injection of BOTOX® and BOTOX® COSMETIC should be discontinued and appropriate medical therapy immediately instituted.

Pre-Existing Neuromuscular Disorders

Caution should be used when administering BOTOX® to individuals with peripheral motor neuropathic diseases (e.g., amyotrophic lateral sclerosis, or motor neuronopathy) or neuromuscular junctional disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome). Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects including severe dysphagia and respiratory compromise from typical doses of BOTOX® COSMETIC. Published medical literature has reported rare cases of administration of a botulinum toxin to patients with known or unrecognized neuromuscular disorders where the patients have shown extreme sensitivity to the systemic effects of typical clinical doses of the same in these cases dysphagia has lasted several months and required placement of a gastric feeding tube.

Dysphagia

Dysphagia is a commonly reported adverse event following treatment of cacinistic cytonia patients with BOTOX®. In these patients, there are reports of cases of dysphagia severe enough to warrant the insertion of a gastric feeding tube. There is also a case report where a patient developed aspiration pneumonia and died subsequent to the finding of dysphagia.

Cardiovascular System

There have also been rare reports following administration of BOTOX® of adverse events involving the cardiovascular system, such as hypotension and decreased cardiac output, which have resulted in death, especially in patients with myasthenia gravis. (See: WARNINGS). New onset or recurrent severe headaches have also been reported after treatment of blepharospasm.

Thyroid Disorder

Following injection of the orbicularis muscle can lead to corneal exposure, persistent epithelial defect and corneal ulceration, especially in patients with VII nerve disorders. (See: WARNINGS). Injection intervals between injections of 3 to 4 months is recommended.

Human Albumin

The first albumin album, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. BOTOX® and BOTOX® COSMETIC contain the same active ingredient in the same formulation.

IMMUNOGENICITY

Patients or caregivers should be advised to seek immediate medical attention if swallowing, injection, infection, tenderness, swelling, erythema or and/or bleeding-brushing may be associated with the injection.

Glabellar Lines

In clinical trials of BOTOX® COSMETIC the most frequently reported adverse events following the use of BOTOX® COSMETIC with a possible relationship to blepharospasm or respiratory infection1, flu syndrome, bl retaining and nausea.

Overall: In placebo treated patients, (N=75) 2% of patients developed adverse events occurring within 24 hours of the injection site. (See: WARNINGS). New onset of headache has also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, a report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

Genetic

The two clinical studies of BOTOX® COSMETIC did not include sufficient numbers of subjects aged 75 or older to determine whether they respond differently or at a greater or lesser rate than younger adults. Therefore, the responder rates appeared to be higher for patients younger than age 65 than for patients 65 years or older. (See: CLINICAL STUDIES)

There were too few patients (N=3) over the age of 75 to allow any meaningful comparisons.

ADVERSE REACTIONS

General:

BOTOX® and BOTOX® COSMETIC contain the same active ingredient in the same formulation. Therefore, adverse events observed with the use of BOTOX® also have the potential to be associated with the use of BOTOX® COSMETIC.

The most serious adverse events reported after treatment with botulinum toxin include rare spontaneous reports of death, sometimes associated with anaphylaxis, dysphagia, aspiration pneumonia and/or other significant morbidity. There have also been rare reports of adverse events involving the cardiovascular system, including arrhythmias and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including pre-existing cardiovascular disease. (See: WARNINGS). New onset of recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established. Additionally, a report of acute angle closure glaucoma one day after receiving an injection of botulinum toxin for blepharospasm was received, with recovery four months later after laser iridotomy and trabeculectomy. Focal facial paralysis, syncope and exacerbation of myasthenia gravis have also been reported after treatment of blepharospasm.

In general, adverse events occur within the first week following injection of BOTOX® COSMETIC and while generally transient may have a duration of several days or months. Localized pain, injection, infection, tenderness, swelling, erythema and/or bleeding-brushing may be associated with the injection.

Percent of Patients Reporting Adverse Events

<table>
<thead>
<tr>
<th>Body System</th>
<th>BOTOX® Cosmetic (N=405)</th>
<th>Placebo (N=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44%</td>
<td>42%</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Skin and Appendages</td>
<td>Skin Tightness</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Tooth Disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special Senses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blepharospasm</td>
<td></td>
<td>3%</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td>Muscle Weakness</td>
<td>2%</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>Hypertension</td>
<td>1%</td>
</tr>
</tbody>
</table>

Adverse Events Reported at Higher Frequency (>1%) in the BOTOX® COSMETIC Group Compared to the Placebo Group

Immunogenicity

BOTOX® COSMETIC may result in the formation of neutralizing antibodies that may reduce the effectiveness of subsequent treatments with BOTOX® COSMETIC by inhibiting the biological activity of the toxin. The formation of neutralizing antibodies in patients receiving BOTOX® COSMETIC has not been well studied.

The critical factors for neutralizing antibody formation have not been well characterized. The potential for antibody formation is related to the dose and number of injections, the number of patients with a history of allergy to any component of the formulation, and the frequency of repeat injections. Patients who have previously developed neutralizing antibodies may have a delayed response to subsequent injections. Risks resulting from the administration of a second dose of BOTOX® and BOTOX® COSMETIC to patients who have previously developed neutralizing antibodies may be increased.

Reference:

Paraneoplastic Pemphigus Associated With Breast Adenocarcinoma

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ABSTRACT

Paraneoplastic pemphigus (PNP) is a blistering, mucocutaneous disease occurring in patients with malignant neoplasms of different origins. Here we are reporting the third case in the literature of PNP occurring simultaneously with breast adenocarcinoma.

Key words:
Adenocarcinoma, bullous disease, autoimmune, malignancy

Introduction

Paraneoplastic pemphigus (PNP) is an autoimmune, blistering, mucocutaneous disease associated with neoplasia. Characteristically, it manifests with erosions and shallow ulcerations of the oral mucosa and polymorphic cutaneous lesions that can be pemphigus-like, pemphigoid-like, erythema multiforme-like, graft versus host disease-like and lichen planus-like.1 Interestingly, different morphologic patterns of skin lesions may be present concomitantly in a patient or may vary during the disease course.2 Most PNP cases are associated with a hematologic malignancy, but cases of solid, non-hematologic neoplasms of different origins can also occur.2 In this report, we present the third case in the literature of PNP occurring simultaneously with breast adenocarcinoma.

Case Report

A 46-year-old Arabic female, a known case of completely resected bilateral breast adenocarcinoma, diabetes mellitus and hypothyroidism, presented to our dermatology clinic with recurrent, slightly painful, shallow, ulcerated, mucocutaneous lesions for the past year. According to the patient, the condition started as recurrent, fluid-filled bullae that ruptured easily, leaving macerated and ulcerated lesions that healed completely. They were mainly located in the mouth, scalp and upper trunk. The patient underwent bilateral radical mastectomy six years prior, oophorectomy and hysterectomy two years prior and had received multiple courses of chemotherapy for her breast adenocarcinoma, of which the last course was four months prior to her presentation. She never received radiotherapy. Since then, she was kept on Fucidin cream and clobetasol dipropionate twice daily for her skin lesions and triamcinolone acetonide in oral paste twice daily for her mouth lesions. On examination, there were multiple ruptured bullae with a few irregularly shaped, erythematous, superficial ulcers affecting the chest and the upper back. In the oral cavity, there were similar, superficial, slightly painful ulcers affecting the gingiva, the floor of the mouth, the tongue, the hard palate and the soft palate. No ocular or vaginal involvement was observed. Two skin punch biopsies were taken at six-month intervals. There were non-specific findings in the first one, which initially biased our diagnosis, but significant findings in the second biopsy revealed acantholysis and mild, superficial, dermal perivascular lymphohistiocytic infiltrate. A biopsy from oral mucosa showed nonspecific ulceration and lymphohistiocytic infiltrate with no intraepithelial lesion or malignancy. Direct immunofluorescence (DIF) from skin, repeated twice, was positive at the epidermal intercellular zone and basement membrane zone. Those clinical and histopathological findings combined with DIF results were suggestive of a diagnosis of PNP. The patient was kept on potassium permanganate soaks three times a day for the weeping lesions, clobetasol dipropionate cream for skin lesions and triamcinolone acetonide in oral paste for oral lesions, both twice daily. After three weeks, the lesions were in the healing phase; but after three months the same bullous lesions recurred, and treatment was repeated.

Discussion

Paraneoplastic pemphigus (PNP) was first defined as a separate blistersing disease in 1990 by Anhalt et al.3 Since then, almost 150 cases have been reported in the literature. Initially, the diagnostic criteria included the following clinical, histologic, DIF, indirect immunofluorescent (IIF) and immunoprecipitation tests:

1. Painful mucosal erosions and polymorphic skin eruptions
2. Histopathologic features of intraepidermal acantholysis, dyskeratosis and vacuolar interface dermatitis
3. DIF findings of intercellular epidermal IgG and complement, with or without granular linear complement deposition along the basement membrane zone
4. Serum antibodies detected by IIF that bind cell surfaces of stratified squamous epithelia, as well as simple, columnar and transitional epithelia
5. Serum immunoprecipitation with a complex of five proteins (desmoplakin-1250 kDa, BP Ag-230 kDa, envoplakin and desmoplakin I-210 kDa and periplakin-190 kDa and 170-kDa)2

These were later revised by Camisa and Helm,4 who divided them into major and minor signs: The major signs include polymorphic mucocutaneous eruption, concurrent internal neoplasia and serum antibodies with a specific immunoprecipitation pattern. The minor signs include histologic evidence of acantholysis, DIF showing intercellular and basement membrane staining, and IIF staining with rat bladder epithelium. Either three major or two major and two minor signs are required for the diagnosis of PNP.2 The existence of a neoplasm is recognized prior to the eruption of PNP in about two-thirds of the cases.5 Clinically, paraneoplastic pemphigus (PNP) manifests with erosions and ulcerations of the oral mucosa plus polymorphic bullous cutaneous lesions which can be pemphigus-like, pemphigoid-like, erythema multiforme-like, graft versus host disease-like and lichen planus-like.1 Isolated oral lesions, as the first sign, are present in 45% of cases,1 while oral involvement is reported in 100% of cases.6 Conjunctival lesions, which can resemble those seen in cicatricial pemphigoid, are present in about two-thirds of the patients.5 Of all reported PNP cases, 84% were associated with hematologic-related neoplasms.7 The non-hematologic neoplasms associated with PNP comprised 16% of all cases, of which 8.6% were epithelial-origin carcinoma,1,7-14 and 6.2% were mesenchymal-origin sarcoma.3,15-21 Of the reported carcinomas, there were adenocarcinoma of the pancreas,11,12 colon,1,12,23 breast13 and prostate;18 squamous cell carcinoma of the tongue19 and vagina;20 and one case of
multiple skin tumors. In the presented case, the patient was initially undiagnosed, but repeated skin biopsies and DIF supported our clinical impression of PNP. She was also a known case of breast adenocarcinoma and was having recurrent mucocutaneous bullous ulcerated lesions, making up two major and two minor PNP diagnostic criteria. Treatment of PNP is difficult, with options including resection of the initial tumor and corticosteroids, sometimes in combination with cyclosporine or cyclophosphamides, azathioprine, mycophenolate mofetil, rituximab and plasmapheresis or immunopheresis. Generally, prognosis is poor, with a mean survival time after initial diagnosis of three months, although occasional patients survived longer. Death usually occurs as a result of respiratory failure or infections. In conclusion, this is the third reported case of PNP occurring in a patient with a preexisting breast adenocarcinoma, which signifies that clinicians should be highly suspicious when signs and symptoms of bullous dermatosis are present in cancer patients of both hematologic and non-hematologic origin.

References

Introduction:

Vitiligo is an acquired cutaneous disorder characterised by circumscribed depigmented lesions due to loss of melanocytes within the epidermis. It affects people of all races, with an incidence of 1–2%.1 and approximately one-half of those patients are below the age of 20 years.2 Epidemiological studies have shown that one quarter to one third of patients with vitiligo have family members affected with the disease.2 There are several hypotheses on the pathogenesis of the disease. Autoimmune Hypothesis is the most important and popular which suggests that abnormalities of the immune system result in destruction of melanocytes. Other hypotheses include neural hypothesis, melanocyte self-destruction hypothesis and biochemical hypothesis. Immunohistochemical studies indicated that T cells are abundant in actively progressing lesions which are mainly CD4+ and CD8+ which express activation molecules such as interleukin-2 receptor (IL-2R). Topical tacrolimus (FK 506) and pimecrolimus (SDZ ASM 981) are known topical immunomodulators (TIMs) which inhibit the activation and maturation of T cells by inhibiting calcineurin function.3-4 In addition, pimecrolimus inhibits transcription and production of IL-4, IL-5, IL-10, IFN delta, TNF alpha and the release of inflammatory mediators from mast cells and basophils.5-7 Studies on the use of tacrolimus in vitiligo have been published5,10,11,12,13,14 but two reports on the use of pimecrolimus in vitiligo have been published so far.15,16 In this trial we explored further the effectiveness of topical pimecrolimus in the treatment of vitiligo.

Objective:

This study was done to evaluate the effect of pimecrolimus 1% cream in the treatment of stable vitiligo.

Methods:

Ten patients with stable vitiligo and who were followed up regularly in our dermatology clinic at King Fahad Hospital of the University in Alkhobar, Saudi Arabia enrolled in this study during the period of December 2004 to November 2005. Their ages ranged between 5-55 years. Nine were females and one was male. Their vitiligo had been present for a duration ranging between 4 months to 15 years. Seven patients were on NBUVB for more than one year while three were not on any treatment due to either the condition was newly diagnosed or past failure of topical steroids and phototherapy. None of our patients had thyroid or parathyroid disease, cardiovascular disease, malignancy, impaired renal or liver function, pregnancy, or lactation. Seven Patients were instructed to apply pimecrolimus 1% cream twice daily on the facial lesions and 3 patients on the knee lesions. Patients who were on NBUVB phototherapy were allowed to continue their scheduled sessions. Response to treatment was recorded by taking photographs of the lesions before and after the start of treatment. Improvement was recorded as minimal (25-50%), moderate (50-75%), marked (75-90%) or complete (90-100%). The cream was stopped if all
the depigmented areas regained the pigment or there was no pigmentation observed for the first 3 months. Side effects related to treatment were reported including burning sensation and atrophy. Patients were followed up at 12-week interval for 12 months.

**Results:**

All of our patients completed the study. Their ages ranged between 5 to 55 years (mean 26 years). The duration of vitiligo varied from 4 months to 15 years (mean 4.9 years). The face and neck were affected in 8 patients, the acral regions in 2 patients, trunk in one patient, and extremities in 6 patients. At the end of the 12 months period, 5 patients (50%) showed complete repigmentation, one patients (10%) showed marked improvement, 3 (30%) showed moderate improvement while one patient (10%) showed minimal improvement. In more than 80% of patients, the onset of the repigmentation was observed within the first 12 weeks. The pattern of repigmentation was diffuse and perifollicular which subsequently progressed to full repigmentation. Other areas which were treated with only NBUVB were responding at a slower rate than the areas treated with both topical pimecrolimus and NBUVB. No patients reported any adverse reactions.

**Discussion:**

There has been a substantial interest in topical pimecrolimus because of its significant anti-inflammatory and immunomodulatory activities and low systemic immunosuppressive potential. Several studies were conducted on patients with vitiligo who responded to treatment with tacrolimus ointment and concluded that tacrolimus ointment may be an efficacious and safe treatment option for vitiligo while others reported similar response with pimecrolimus cream. In this study we have provided evidence that application of pimecrolimus 1% cream is effective in the induction of repigmentation in vitiligo either used alone or with NBUVB. Additionally, it may promote faster repigmentation of vitiligo with NBUVB making it a good addition to the treatment regime with NBUVB. The most logical explanation for this clinical response is the immunomodulatory effect of pimecrolimus exerted locally at the vitiliginous lesions. Besides, considering the lack of atrophogenic potential and ocular cataracts or glaucoma with pimecrolimus cream makes this agent suitable for treating vitiligo of the face. In conclusion, this study showed that topical pimecrolimus is an effective and safe treatment option for stable vitiligo and we recommend larger prospective studies to explore further the efficacy of pimecrolimus cream in different types of vitiligo and in patients with extensive lesions.

**References:**

A Review of Mohs Micrographic Surgery: Common Indications


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ABSTRACT

Background: Mohs micrographic surgery (MMS) is a highly effective surgical modality for removal of aggressive tumors, recurrent tumors, or tumors located in the high-risk anatomic locations. MMS is founded on the idea of excision with minimal margins and immediate histologic examination where the dermatologist acts as a surgeon and pathologist. Method: We reviewed the literature regarding clinical and pathological considerations for MMS. We also explored the most common tumors, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), treated with MMS with respect to their cure rates and cost effectiveness compared to non-Mohs modalities. Results: The results showed the five-year cure rates for primary BCC treated with MMS compared to non-Mohs modalities to be 99% versus 93.5%, respectively. Recurrent BCC treated with MMS had a 94.4% cure rate compared to non-Mohs at 80%. MMS cure rates for primary SCC were found to be 96.6% as opposed to non-Mohs modalities at 92.1%. The recurrent SCC cure rates were 90-93.3% for MMS versus 76.8% with non-Mohs modalities. Cost analysis illustrated MMS charges were comparable to non-Mohs modalities. The results showed the average cost of MMS to be $1,243 versus $1,167 for excision with permanent section margin control, $1,400 for excision in the office with frozen section margin control, and $1,973 for excision with frozen section margin control in an ambulatory surgical facility. Conclusions: MMS is a meticulous modality that can effectively excise high-risk basal cell carcinoma and squamous cell carcinoma tumors. It relies on horizontal sectioning to visualize all peripheral and deep tumor margins. MMS is a cost-effective technique that ensures maximal tissue preservation while producing the highest cure rates of primary and recurrent cutaneous tumors.

Historical Perspective

Frederick E. Mohs, a general surgeon, first introduced the Mohs micrographic surgery (MMS) technique in the 1930s at the University of Wisconsin. Mohs micrographic surgery was originally described as Mohs chemosurgery due to the application of 20% zinc chloride paste fixed to the cancerous skin to adhere it in-situ prior to surgical removal of the tissue.1 In 1941, Dr. Mohs was able to show the efficacy of this revolutionary fixed-tissue technique on eyelid cancer. He reported a high five-year cure rate of 98% and 98.1% for basal cell carcinoma and squamous cell carcinoma, respectively. The fixed-tissue technique begins with delineating the tumor outline and debulking the tumor with a curette or scalpel. Dichloroacetic acid is applied to the debulked area to promote penetration of zinc chloride paste. The paste is applied to the tissue for six to 24 hours to enhance tissue fixation in-situ. A thin, pie-shaped layer of tissue can then be excised in an outpatient setting for processing and microscopic examination.2 If the histological margins are positive, then the above process would be repeated. Because the Mohs fixed-tissue technique was a surgical procedure, Dr. Mohs published his first five reports in surgical journals; however, few surgeons elected to utilize this novel technique. Conversely, after Dr. Mohs published an article on “Chemosurgical treatment of cancer of the face” in a dermatology journal, the technique received great popularity among dermatologists. Although the original fixed-tissue technique was reliable, it was very time-consuming, laborious, uncomfortable, and oftentimes painful. Thus, in the 1970s, doctors Theodore Tromovitch and Samuel Stegman modified the popular Mohs technique with the utilization of horizontal frozen sections rather than fixed tissue.3 The fresh-tissue technique utilizes local anesthesia for controlled excision of the tumor within a single day. Except for the application of the 20% zinc chloride fixative, the fresh-tissue technique follows the same processes as the original Mohs technique. Advantages of the fresh-tissue technique include elimination of the perioperative pain produced by the fixative, the ability to perform multiple excisions in one day, and elimination of the post-fixation slough, which had precluded immediate reconstruction.4 Summary of the Mohs micrographic surgery using the fresh-tissue technique is illustrated in table 1.5-10

Since the inception of Mohs micrographic surgery was introduced over seven decades ago, it has developed into a subspecialty of dermatology. Although there are other subspecialists who practice MMS, dermatologists are uniquely suited for this procedure given their training in dermatopathology, cutaneous oncology, and cutaneous surgery. Initially, training was informal, lasting from days to months through Dr. Mohs’ Chemosurgery Clinic and through his trainees. Currently, there are several pathways to receive Mohs micrographic surgery training. The first pathway is through the American College of Mohs Micrographic Surgery and Cutaneous Oncology (ACMMSCO), established in 1967.14 There are approximately 60 approved programs. The second pathway is through the American Society for Mohs Surgery (ASMS), established in 1990. The ASMS was established to provide professional and educational support for non-ACMMSCO trained Mohs surgeons.15 The third pathway is through the Accreditation Council for Graduate Medical Education (ACGME) Procedural Dermatology Fellowship training program, established in 2003.16 This fellowship program consists of 12 months of advanced dermatologic training that provides surgical training beyond the scope that is expected in a dermatology residency training program, including training in Mohs micrographic surgery, cutaneous reconstruction of surgical defects, sclerotherapy, chemical peel, hair transplantation, dermabrasion, small-volume liposuction, cutaneous soft tissue augmentation with injectable filler material, laser surgery, and rhinophyma correction cutaneous oncology.17 All of the above MMS programs are considered training or fellowship without certification through the American OTC Board of Dermatology. However, the American Osteopathic Board of Dermatology (AOBD) offers a Certificate of
Added Certification in MMS for eligible AOBD boarded dermatologists. 

**Clinical Considerations for MMS**

The most compelling indication for MMS is recurrent tumors, due to their unpredictable growth patterns along surgical scars and through low-resistance planes such as subcutaneous and muscle tissues. These unstable growth patterns are harbingers for subclinical extension. The high peril zone for recurrence and metastases is skin overlying cartilage and bony structures especially in the preauricular area, retroauricular sulcus, nasolabial fold, inner canthus, philtrum, temple, upper lip, nose, and eyelid. Because recurrent tumors possess aggressive growth patterns, they have higher risk of recurrence and metastases; therefore, conventional excisional methods are not recommended, for they are unreliable. Hence, MMS is the treatment of choice for recurrent tumors located in these high-risk areas. Additionally, an important location for MMS indication is where tumor growth is in a cosmetically or functionally important area such as the genitals, fingers, and toes.

Other common clinical considerations for MMS are tumor size, poorly defined tumors, and tumors with positive margins after conventional excision. A large primary skin cancer lesion is defined as greater than 2 cm on the trunk or the extremities and greater than 1 cm on the face. Due to the direct correlation of tumor size and location with high risk of recurrence and metastases, MMS is the treatment of choice for these tumors. Poorly defined tumors imply subclinical spread and risk of recurrence. Thus, if conventional excision were used, wide margins would be required to prevent recurrence, which would sacrifice normal skin. For these reasons, poorly defined tumors are treated with MMS in order to provide complete evaluation of the specimen and spare healthy tissue. Finally, tumors with positive margins are indicated for MMS because scar from the previous treatment creates a low-resistance pathway for deep-tissue infiltration of malignant cells, which exhibits unrecognized spread (Table 2).

**Pathological Considerations for MMS**

In 1835, Jean Cruveilhier, a French pathologist, described the first perineural spread of tumor cells in a mammary carcinoma that spread along the facial nerve. Since then, perineural spread has been well-documented in a wide variety of malignant neoplasms such as carcinomas of the prostate, rectum, and parotid. Although cutaneous perineural invasion has been widely recognized, its prevalence is rare. Perineural invasion carries a high risk of recurrence and metastases and is more common in squamous cell carcinoma (SCC) than basal cell carcinoma (BCC), with reported incidence of 2.5 to 14% and 0.178%, respectively. Rowe et al. reported that SCC with perineural spread elicited a local recurrence rate of 47.2% and a metastatic rate of 47.3%. Furthermore, he compared conventional excision versus MMS in the treatment of neurotropic SCC, which displayed a local recurrence rate of 47.2% and 0%, respectively. Patients with tumors of the face who exhibit perineural invasion may never experience symptoms of pain, numbness, paraesthesia, facial paralysis, diplopia, blurring vision, or decreased corneal reflexes. In fact, 60 to 70% of patients with perineural invasion are asymptomatic. It is important to recognize that adjuvant radiation therapy is recommended for post-surgical excision of perineural tumors due to their unpredictable surgical margins and high possibility of recurrence and metastases (Figures 1 – 2).

**Table 1. Method for fresh-tissue technique sequence**

1. The patient is prepped, and the treatment site cleansed.
2. The Mohs surgeon outlines the tumor with a marking pen before the administration of local anesthesia.
3. The tumor is debulked with curette or scalpel to define the borders of the tumor.
4. The tumor is excised with a 2-4mm margin of normal skin around the curetted site with a standard or flexible scalpel at a 45-degree angle. Hatch marks are placed to orient the tissue.
5. The excised specimen is removed and placed on gauze, oriented relative to the patient.
6. A map of the excised tissue in relation to the patient is drawn.
7. The specimen is transported to the laboratory and cut into quadrants (if indicated).
8. A Mohs micrographic technician prepares and stains the slides. The tissue is placed upside down (deep surface facing up into the cryostat). The frozen tissue is then sectioned into 5-7um thickness. The sliced tissue is placed on the slide, ready to be stained. Hematoxylin-eosin is the most commonly used stain, followed by toluidine blue.
9. The Mohs surgeon reviews the horizontally processed slides with the map in hand to mark any residual tumor that is identified. The location of residual tumors is marked on the map.
10. The residual tumor is excised, but only those areas that contain tumor. The tissue is then re-processed as stated in steps 4 through 8.
11. Reconstructive plans are made according to the location and extent of the defect. Wound repair can be immediate or delayed. Healing of tissue can be second intention, primary closure, flaps, grafts, or combined closure.

**Table 2. Clinical Considerations for MMS**

1. Recurrent tumors
2. Tumors located in tissue-preservation areas, such as genitals, fingers, toes, and face
3. Tumor size greater than 2 cm on trunk and extremities or greater than 1 cm on face
4. Tumors with positive margins
tumor. Although BCCs rarely have metastatic potential to effectuate the death of the patient, certain subtypes of BCCs possess unpredictable spread beyond clinical margins with high risk for recurrence and metastases, such as infiltrative, morpheaform, micronodular, and metatypical types.27-38

Currently, BCCs are the most common skin cancer in the United States, with an estimated frequency of over 900,000 cases per year.28 Because BCCs are the most common cutaneous tumors, they constitute the highest number of cases for MMS. Studies have revealed the five-year cure rate of primary tumors to be 99% with MMS compared with a 96% cure rate with recurrent BCCs.8,9,20 Additionally, according to Rowe et al., the five-year recurrence rate for non-Mohs procedures was 8.7 times higher than recurrence rates for MMS when treating primary BCCs. Comparing MMS with other non-Mohs procedures, the five-year recurrence rate of primary BCCs treated by MMS was 1%, 7.5% for cryosurgery, 7.7% for curettage and electrodessication, 8.7% for radiation therapy, and 10.1% for surgical excision (Table 4).20 Rowe’s study of the five-year recurrence rate for primary BCCs treated with surgical excision corroborated Silverman et al.’s study, which had a recurrence rate of 10.6%.40

As for the treatment of recurrent BCCs, the recurrence rate was 5.6% with MMS as compared to the average 19.9% when treated with non-Mohs modalities.20 For BCCs less than 3 cm, the cure rate was over 99%; however, if the tumor was greater than 3 cm, the cure rate dropped to 93%.9 The lower recurrence rates for MMS as compared to surgical excision were best justified by the Mohs surgeon’s meticulous examination of all of the lateral and inferior margins of the resected tissue via horizontal sectioning technique as compared to the random examination of inferior and lateral margins when the pathology lab “bread loaves” the sections after surgical excision.20

Basal cell carcinomas that are indicated for MMS have the aggressive subtypes, such as infiltrative, morpheaform, and micronodular. The term infiltrative was first described by Thackray in 1951 as a histologic subtype of BCC that he felt was more difficult to eradicate than nodular BCC.41 Years later, Sexton et al.’s study illustrated that infiltrative BCC was more likely to have positive margins after simple surgical excision than nodular BCC, 26.5% versus 6.4%, respectively.42 Clinically, infiltrative BCC’s tumor masses are usually small with irregular, spiky, or jagged borders.42 Histologically, the infiltrative subtype is made up of small cords and nests that disperse by small, finger-like extensions, which can permeate through tissue without much displacement.42 Thus, positive margins and recurrence are more likely to occur.

The morpheaform subtype BCC has been clinically described as solitary, flat, ill defined, smooth, yellowish plaque, or slightly depressed indurated plaque (Figures 3 - 4).43,44,45 Mora morphemaform’s clinical extension is indistinctive, thus making it extremely difficult to assess its true margin with simple surgical excision. Histologically, morphemaform has been referred to as the “iceberg epithelioma” due to its infiltrating ribbons and tentacles of neoplastic cells that vary from small aggregations to one or two cells embedded in dense, concentrically arranged fibrous stroma that tend to grow laterally and deeply away from the main clinical neoplastic mass.45,46,47 Salasche et al.’s 49 study of 51 morpheaform cases found the average exten-
Figure 3  Morpheaform basal cell carcinoma of the left lower lip margin, pre-operative size of 1.7 x 1.5 cm

Figure 4  Status post five stages of MMS for morpheaform basal cell carcinoma of the left lower lip margin, defect size 4.6 x 3.0 cm

Figure 5  Squamous cell carcinoma on right temple with MMS, preoperative size 2.2 x 1.6 cm

Figure 6  Squamous cell carcinoma on right temple status post two stages of MMS, defect size of 2.5 x 2.2 cm

As clinical features of erythroplasia of Queyrat, it usually presents with a sharply demarcated, velvety, erythematous, moist, and shiny patch on the inner surface of the prepuce and glans penis. Histologically, the epidermis of SCC in-situ shows hyperkeratosis, parakeratosis, and broad acanthosis or anastomosis of adjacent rete ridges. The atypical epidermal layer may produce the "flip sign," whereby the epidermis has lost its polarity to the point that the superficial epidermis resembles the deeper epidermis; thus, if you flip the tissue upside down and microscopically examine it, you would barely notice the difference between the superficial epidermis and the deeper epidermis.21,22

SCC in-situ may be treated with cryotherapy or topical 5-fluorouracil; however, there is a high rate of recurrence. Imiquimod 5% cream has been an effective therapeutic option, with an efficacy rate as high as 90%. MMS is usually the treatment of choice when preservation of normal tissue is critical, such as with lesions located on the face, digits or penis or when lesions are greater than 2 cm on the trunk.23

Squamous Cell Carcinoma:

Squamous cell carcinoma (SCC) is currently the second most common type of nonmelanoma skin cancer.24 For the past two decades, the incidence of SCC has steadily risen due to the increase in sun exposure of the general population. Sun-exposed SCCs metastasize in less than 1% of the cases; however, the incidence is higher on the lip, in sun-covered areas, and in neoplasms greater than 1.0 mm thick.25 Additionally, SCCs’ risk of metastases depends on the size, depth of invasion, differentiation, anatomical location, neurotropism, host immunosuppression, and recurrence after previous treatment.26 The risk of metastases in primary SCC has been reported to range from 2.5% to 5%, whereas recurrent tumors are reported to have a metastatic rate of 30%.19,27

In the United States, the annual SCC incidence is estimated to be 1 case per 1,000 individuals, which approaches to about 250,000 cases per year.25 Clinically, SCC frequently arises at the site of actinic keratosis on sun-exposed areas such as the face and back of hands (Figures 5 - 6). Well-differentiated SCCs may present with indurated hyperkeratotic nodules or plaques that may also become eroded or ulcerated. However, undifferentiated SCCs appear as red, soft, fleshy, granulatating, friable papules or nodules. Histologically, a well-differentiated SCC shows paler epithelial proliferation with a greater number of keratin pearls or squamous eddies and is less atypical.28 A poorly-differentiated SCC shows more aggressive and infiltrative behavior. It shows less paler epithelial proliferation with sparse keratin pearls and more severe atypical cells.23

Primary SCC is the second most common skin cancer treated with MMS, which has a five-year local cure rate of 96.9% compared to the five-year local cure rate of 92.1% with non-Mohs modalities.29 For recurrent SCCs, MMS is associated with a five-year cure rate of 90 - 93.3% as compared to 76.8% for non-Mohs modalities.30 Other than MMS, conventional excision has been the long-time standard of care for SCC, with a 91.9% cure rate; however, as previously discussed, this technique sacrifices more normal skin to obtain clear margins. For well-differentiated SCC, the cure rate for non-Mohs modalities is 81% versus 97% with MMS. Poorly-differentiated SCCs significantly decrease the cure rate, with MMS at 67.4% versus non-Mohs modalities at 46.4% (Table 5).31 Another non-Mohs modality in the treatment of SCCs is radiation therapy. Adjuvant radiation therapy has been utilized in the treatment of both superficially invasive and moderate-to-high-risk SCCs in the geriatric population that is not eligible for surgery. Additionally, it is also used as adjuvant therapy for neurotropic SCCs and for patients with a high risk of recurrence after surgery.32,33 As for cryotherapy in the treatment of SCCs, it should only be utilized for superficially invasive SCCs or SCCs in-situ that are less than 2.0 cm, because it offers no histologic margin control.34,35,36

46  A REVIEW OF MOHS MICROGRAPHIC SURGERY: COMMON INDICATIONS
Cost Analysis of MMS

Non-melanoma skin cancers (NMSCs) are the most common type of cancer in the United States, with approximately 1.3 million cases diagnosed annually. In the United States, one in two men and one in all Medicare cancer expenditures. For this sheer numbers they represent about 5% of to 2,500 deaths annually, due to NMSCs’ of cutaneous malignancies; therefore, they a cost-effective modality for the treatment of MMS due to its cost. Many investigators have questioned defacto size; therefore, it decreases the cost of mal tissue and decreases the operative problem surgery in their prospective evalu-

Table 6. Average Cost Analysis Summary of 400 Consecutive Patients

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mohs Micrographic Surgery</td>
<td>$1,243</td>
</tr>
<tr>
<td>2. Excision with Permanent Section</td>
<td>$1,167</td>
</tr>
<tr>
<td>3. Excision in Office with Frozen Section</td>
<td>$1,400</td>
</tr>
<tr>
<td>4. Excision in Ambulatory Facility with Frozen Section</td>
<td>$1,973</td>
</tr>
</tbody>
</table>

Safety Data of MMS

The field of dermatologic surgery has flourished over the past several decades. A survey by the American Society for Dermatologic Surgery predicated that its members performed approximately 3.9 million procedures, of which 1.4 million were outpatient cutaneous surgeries. Thus, due to the increased trend toward outpatient cutaneous surgeries, it is important for dermatologists and dermatologic surgeons to thoroughly characterize the safety of office-based surgery. Cook and Perone have shown the safety associated with outpatient surgery in their prospective evaluation of the incidence of complications (postoperative hemorrhage, hematoma for-

References:

TRAN, NGUYEN, CONTE 47
For anywhere there’s acne, there’s EVOCLIN.

Finally, an acne formulation that’s easy to apply over multiple body areas. EVOCLIN comes in a patient-preferred foam vehicle, with minimal residue. It’s effective in reducing inflammatory and noninflammatory lesions. Plus it’s safe and well tolerated. Looking for a treatment that works anywhere there’s acne? EVOCLIN is here.

EVOCLIN is a once-a-day topical clindamycin foam for the treatment of acne vulgaris. The most common adverse events were headache (3%) and application-site reactions including burning (6%), itching (1%), and dryness (1%). EVOCLIN is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, or a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis. Diarrhea, bloody diarrhea, and pseudomembranous colitis have been reported with systemic and rarely with topical clindamycin. Discontinuation is recommended if diarrhea develops.

Please see following page for full prescribing information. For further details, visit www.evoclin.com.
Evoclin (clindamycin phosphate) Foam, 1%.

For acne anywhere.

The chemical name for clindamycin phosphate is methyl 7-chloro-6,7-dihydro-6(1H)-methyl-2-(4-propyl-2-pyrrolidinecarboxamido)-1-thio-l-threo-(clindamycin phosphate) Topical Gel, 1%, once daily for five days and AUC(0-12) were 23% and 9% lower, respectively, for Evoclin Foam than for Clindagel® Topical Gel, 1%, once daily for five days. On Day 5, the mean Cmax for Evoclin containing clindamycin phosphate equivalent to 10 mg clindamycin per gram, is 1% of Subjects

<table>
<thead>
<tr>
<th>Efficacy Parameters</th>
<th>Evocin Foam N=266</th>
<th>Vehicle Foam N=127</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment response (ISGA)</td>
<td>31%</td>
<td>18%*</td>
</tr>
<tr>
<td>Percent reduction in lesion counts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory Lesions</td>
<td>49%</td>
<td>35%*</td>
</tr>
<tr>
<td>Noninflammatory Lesions</td>
<td>38%</td>
<td>27%*</td>
</tr>
<tr>
<td>Total Lesions</td>
<td>43%</td>
<td>31%*</td>
</tr>
</tbody>
</table>

INDICATIONS AND USAGE
Evoclin is indicated for topical application in the treatment of acne vulgaris. In view of the possibility of inducing diarreha, bloody diarrhea, and pseudomembranous colitis, the physician should consider whether other agents are more appropriate. (See CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS.)

CONTRAINDICATIONS
Evoclin is contraindicated in individuals with a history of hypersensitivity to preparations containing clindamycin or lincomycin, a history of regional enteritis or ulcerative colitis, or a history of antibiotic-associated colitis.

WARNINGS
Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in patient death. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral clindamycin. Severe diarrhea has resulted in death. These reactions have been reported with the use of topical and systemic clindamycin. Inflammatory Lesions 49% 35%*

Treatment response (ISGA) 31% 18%*

Percent reduction in lesion counts

Inflammatory Lesions 49% 35%*

Noninflammatory Lesions 38% 27%* Total Lesions 43% 31%* 5/24 P<.0001

To Use Evoclin:
1. Do not dispense Evoclin directly onto your hands or face, because the foam will begin to matt on contact with warm skin.
2. Remove the clear cap. Align the black mark with the nozzle of the actuator.
3. Hold the can at an upright angle and then press firmly to dispense. Dispense an amount directly into the cap or onto a cool surface. Dispense an amount of Evoclin that will cover the affected area. If the can seems warm or the foam seems runny, run the can under cold water.
4. Pick up small amounts of Evoclin with your fingers and gently massage into the affected areas until the foam disappears.

In a contact sensitization study, none of the 238 subjects developed evidence of allergic contact sensitization to Evoclin. Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in patient death. Therefore, it should be used with caution in patients receiving such agents.

Drug Interactions:
Orally and parenterally administered clindamycin has been associated with severe diarrhea. Antiperistaltic agents, such as opiates and diphenoxylate with atropine, may cause obstipation and predispose to the passage of blood and mucus. Endoscopic examination may reveal ulceration of the terminal portion of the ileum. Use of the topical formulation of clindamycin results in absorption of the antibiotic from the skin surface. Diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral clindamycin. In a contact sensitization study, none of the 238 subjects developed evidence of allergic contact sensitization to Evoclin. Orally and parenterally administered clindamycin has been associated with severe colitis, which may result in patient death. Therefore, it should be used with caution in patients receiving such agents.

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Eruptive Vellus Hair Cysts: A Case Report and Literature Review

Amy M. Broomer, D.O.*, Stanley E. Skopit, D.O., FAOCD**
*3rd Year Resident, NOVA Southeastern University/BGMC
**Program Director, NOVA Southeastern University/BGMC

ABSTRACT

Eruptive vellus hair cysts is a rare condition that presents in children and young adults. These small papules usually appear on the chest. Treatment options include keratolytics, and rarely, the lesions spontaneously regress. This paper will review the clinical presentation, histology, and pathophysiology of eruptive vellus hair cysts.

Overview

Eruptive vellus hair cysts (EVHC) were first described by Easterly et al in 1977.1 Understanding of this entity has greatly increased over the years. Multiple lesions are referred to as “eruptive” vellus hair cysts, although solitary cysts are occasionally seen. Lesions are most commonly seen on the chest; however, they can be present on the face, neck, extremities, abdomen, back, buttocks, and groin.2 Clinically, these lesions can present with a variety of colors and shapes. Color variations include skin color, yellow, red, brown, gray, and black.3 These small lesions, usually 1 to 3 mm, may appear as papules (with or without inflammation), umbilicated lesions, or open, comedone-like lesions.4

Case Report

A 14-year-old Indian female presented with a one-year history of papular eruption on the legs and abdomen. Multiple follicular papules, as well as open comedones, were seen on the lower extremities and the abdomen (Figs 1 and 2). Numerous erythematous papules were noted, as well as the occasional gray papule; lesions were 1 to 2 mm in size. The patient’s medical history was unremarkable; however, the family history was positive in the father for keratosis pilaris on the posterior aspect of the upper extremities. The patient was taking no medications except for salicylic acid 6%, started one week prior to being seen in the clinic. Mild improvement was noted by the patient with the salicylic acid. The biopsy that was performed was stained with hematoxylin and eosin (Fig 3). Histology revealed an infundibular cyst with vellus hairs, hyperkeratosis and inflammation.

Vellus hair cysts are usually located in the middle-to-upper dermis. Histologically, these lesions are lined by stratified squamous epithelium with an attenuated granular layer. Loose, laminated keratin with the numerous characteristic vellus hairs were seen within the cyst. Rarely, other structures can be observed in the cyst wall, such as melanocytes, langerhan cells, and small arrector pili muscles attached to the outer cyst wall.5 Some cysts connect with the surface of the epidermis, forming an open pore containing keratin and vellus hairs.6 It is unclear whether these open pores are the initiating process in cyst formation or the end stage with extrusion of the contents and resolution. In specimens where the cysts had almost disappeared, foreign-body granuloma with giant cells containing vellus hairs were observed.7

There are many reports in the literature of EVHC seen in conjunction with steatocystoma multiplex8,9 and pachyonychia10. Both of these conditions have been associated with mutations that encode keratin 17, as does EVHC.11 Some individuals express a dominant inheritance,12 while others appear to be more congenital.13 The exact progression of this entity is poorly understood. Easterly et al. postulated that the development of the cyst was initiated by the loss of epidermal contact, allowing for the retention of the keratinous material and hairs.14 They also postulated that a keratotic plug at the follicular infundibulum deflected hairs to the deeper part of the follicle, which caused the dilation in which several hair roots of a compound follicle unit have a common infundibulum. There is much to be learned to complete our understanding of EVHC.

Although EVHC has presented from birth to those in the sixth decade of life, it most commonly appears in children or young adults.15 There does not appear to be any racial predilection or gender bias. These lesions are not associated with any subjective symptoms.16 Clinically, EVHC should be differentiated from acneiform eruptions, folliculitis, perforating disorders, and keratosis pilaris. Treatment is symptomatic. Rarely, some individuals have complete remission of their lesions.17 Therapeutic modalities include retinoids, lactic acid, incision and drainage, needle evacuations, and CO2 or erbium:YAG laser ablation.18

Conclusion

Eruptive vellus hair cysts is an uncommon disease that usually manifests in
childhood and can spontaneously clear without sequelae. Many patients do not seek medical evaluation because of its innocuous nature, and it is probably under-diagnosed. Additionally, its asymptomatic nature reduces the number of biopsies that are performed, and its clinical similarity to other benign entities increases the risk of misdiagnosis.

Acknowledgements

I would like to thank Dr. Raymond Barnhill, Dr. Andrew Hanly, and Dr. Evangelos Poulos at Global Pathology Laboratory Services for providing the histological images in this case report.

References:


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A Case Study of ANA Negative Minocycline-induced Lupus

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* First Reconnaissance Battalion, Camp Pendleton, CA
** Staff Dermatologist Branch Medical Clinic Miramar, San Diego, CA

*The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

ABSTRACT

Minocycline-induced lupus is an uncommon condition marked by articular complaints, malaise, fever, weight loss, and positive laboratory findings. This is a case study where the classic presentation of minocycline-induced lupus was present without the supportive laboratory findings.

Introduction

Minocycline is a semi-synthetic derivative of tetracycline used in the treatment of numerous diseases. Minocycline is very lipophilic, penetrates easily into most tissues, binds to the 30S subunit of the bacterial ribosome, and is bacteriostatic, making it a good antibiotic to treat a variety of infectious diseases. Minocycline also has numerous anti-inflammatory properties that make it a versatile drug for treating many different inflammatory diseases such as rheumatoid arthritis and bullous dermatoses. It is a fairly non-toxic drug; but like any other pharmaceutical, it can produce a number of side effects including a hypersensitivity reaction that mimics systemic lupus erythematosus, SLE. This syndrome is called drug-induced lupus syndrome, DIL; when minocycline is the cause, it has been referred to as minocycline-induced lupus, MIL. 2

Case Study

History

A 30-year-old Caucasian male presents to the clinic with chronic, mild-to-moderate nodulocystic acne covering approximately 50% of his face and neck. Over the past five years he has been treated with a variety of products and in a variety of combinations to include benzoyl peroxide gels, topical clindamycin, metronidazole gel, localized steroid injections, and a variety of topical retinoids. None of the treatments produced greater than 50% improvement. Doxycycline 100mg PO BID was started along with QAM benzoyl peroxide and QHS topical retinoids. After six months, doxycycline was discontinued due to inadequate results and moderate gastrointestinal side effects. Minocycline 100mg PO BID was then started.

After one month of treatment with minocycline, there was a dramatic reduction in number and size of nodulocystic lesions. However, after three months he started to complain of mild arthritic symptoms in bilateral elbows. Treatment was continued with follow-up in two weeks. After two weeks, most of the arthritic symptoms shifted from his elbows to bilateral wrists and hands. He also complained of fatigue and malaise to the point of decreased ability to perform any degree or amount of exercise. As an avid exerciser, this is the first time in his life any of these symptoms had been present. A complete history and physical examination was conducted.

Complete review of systems was negative except for complaints of joint pain, morning stiffness, fatigue, and malaise. The joint pain would wake him up in the middle of the night with 7 out of 10 pain and progressively decrease throughout the day with a reported 4 out of 10 pain in the evening.

Differential Diagnosis

The differential diagnosis for a migratory polyarthritis is extensive: rheumatic fever, rheumatoid arthritis, primary amylodosis, hypogammaglobulinemic arthritis, hyperimmunoglobulin D, hemochromatosis, hypothyroidism, hyperparathyroidism, HIV arthritis, syphilis, parvovirus arthritis, pancreatic cancer, hepatitis, primary biliary cirrhosis, Lyme disease, SLE, DIL, and a host of other disease processes.

Physical Examination

An objective examination revealed stable vital signs, stable weight from one year prior, and unremarkable heart, lung, abdominal, neurological, musculoskeletal, and dermatological examinations.

Assessment and Plan

The patient was diagnosed with migratory polyarthropathy of unknown etiology. Minocycline was discontinued. The patient was given an orthopedic consultation, laboratory and radiologic studies were ordered and the patient was instructed to return in two weeks or sooner if new problems developed.

Follow-up and Revision of Diagnosis

Two weeks later, the patient returned to the clinic with a 90% reduction in arthritic and morning stiffness symptoms. He was still experiencing malaise and fatigue. Orthopedic evaluation was normal. Laboratory values and radiographs including peripheral smear, ANA, ENA, TSH, LFT, P-ANCA, ESR, RF, HIV, PPR, UA, Lyme antibody titers, and bilateral wrist and hand radiographic series were all within normal limits.

The patient was instructed to restart the minocycline, although some sources recommend against re-challenging a patient with the inciting drug. He was told to discontinue treatment if his symptoms reappeared. Within two days of restarting the minocycline, the arthritic symptoms returned. The patient stopped the medication and all symptoms were completely resolved two weeks later. The patient was diagnosed with drug-induced lupus, DIL, caused by minocycline. He has been instructed not to take minocycline in the future.

Definition of Drug-induced Lupus

The definition of drug-induced lupus is still somewhat nebulous as there are still relatively few reported cases, 50 as of summer 2000. However, it is generally agreed upon that to diagnose DIL the patient must have at least one lupus-like symptom, positive ANA (usually greater than 1:1280), and resolution of symptoms with discontinuation of drug exposure. To more accurately diagnosis DIL, the patient must possess four of the 11 SLE-specific findings while taking a medication which is known to cause ANA positively or DIL. However, there is wide variation in the degree and amount of positive laboratory

54 A CASE STUDY OF ANA NEGATIVE MINOCYCLINE-INDUCED LUPUS
values in DIL, thus making the absolute definition more complicated.9

DIL differs from SLE in two key areas: DIL is often less severe than SLE; and DIL’s ANA antibodies are usually of the deoxyribonucleoproteins, or antihistones, variety rather than against double-stranded DNA antibodies as in spontaneous SLE. After discontinuation of the inciting drug, ANA titers can take as long as 12 months to return to normal for DIL (typical time course is four months) but usually remain positive for spontaneous SLE.6,8 DIL also has no predilection for sex, whereas spontaneous SLE affects nine times more women than men.9

Typically, DIL has been associated with medications like procainamide and hydralazine. However, an increasing number of drugs are being associated with the syndrome. Minocycline is listed as a definite cause in Cecil’s Textbook of Medicine, while Habif lists it in the category of “drugs recently reported to cause DIL.”5,6

When patients are considered to have DIL by drugs that are widely accepted as causes, i.e. procainamide and hydralazine, the ANA is positive between 90-95% of the time. In these situations, the clinician has to diagnose based on clinical course and symptomatology, not on lab values.4,6

**Manifestations of Drug-induced Lupus**

Articular complaints are present 80% of the time, with arthralgias or myalgias being more prevalent than arthritis. Other common presenting symptoms are malaise, fever, and weight loss.4,5 Usually, symptoms resolve rapidly with the discontinuation of therapy, although some case reports have suggested the time line can be as long as two years. This small case study proposed that re-challenging patients with minocycline usually results in the return of original symptoms within 24-72 hours.9

A systematic review of 57 cases of minocycline-induced lupus found that all patients had polyarthritis/polyarthralgia and a positive ANA. Twelve of the 57 cases had a dermatologic manifestation (non-specific rash, livedo reticularis, oral ulcerations, subcutaneous nodules, or alopecia).10 Habif states that between 25-53% of patients will have dermatologic manifestations, although this usually does not include alopecia, a butterfly rash, discoid lesions, or mucosal ulcers.6

**Treatment**

The offending drug must be removed. Treatment of DIL is supportive for symptomatic complaints. NSAIDS are most frequently used to control the arthralgias. Occasionally, corticosteroids are used if the side effects are severe.1 Note however that DIL normally does not have life-threatening consequences.

**Conclusion**

Doubts may be raised whether our patient had minocycline-induced lupus due to the lack of positive ANA that is almost always present in these cases. However, the patient’s return of symptoms within 48 hours of restarting the minocycline and resolution of symptoms after stopping the drug makes a compelling case in favor of this diagnosis. Two weeks after cessation of the drug from the re-challenge, all symptoms resolved and have not returned. It is our opinion that this is a case of ANA-negative MIL and serves as a reminder to consider this diagnosis despite a negative ANA.

**References**

Cholesterol Embolization Syndrome: Case Report and Review of the Literature

Brian S. Walther, D.O.* and Stephen M. Purcell, D.O.**

* Brian S. Walther, D.O., is a resident in dermatology at Lehigh Valley Hospital, Allentown, Pennsylvania
** Stephen M. Purcell, D.O., is the chairman and program director of the Lehigh Valley Hospital/PCOM Dermatology Residency Program, Allentown, Pennsylvania

ABSTRACT

Cholesterol embolization syndrome (CES) is a disseminated atherosclerotic disease with frequent cutaneous involvement. Risk factors include invasive vascular procedures as well as anticoagulant and thrombolytic therapies. Cutaneous manifestations are variable, but CES most commonly presents as livedo-reticularis. Diagnosis is predicated on clinical findings, laboratory evaluation and histopathology of cholesterol clefts within dermal vessels. Despite surgical and medical intervention, CES has an overall high morbidity and mortality rate.

Case Report

An 82-year-old Caucasian female presented with a progressive onset of painful nodules and ulcerations of both her legs and lower back. Two weeks prior to her visit, she underwent angiography with stent placement after she developed ischemic colitis following identification of a high-grade stenosis of her superior mesenteric artery. Subsequently, she developed painful nodules on her inner thighs and lower back, some of which became necrotic. The patient denied any associated constitutional symptoms or history of similar lesions. Clinical examination revealed a 6-cm, indurated, ill-defined, subcutaneous nodule with central necrosis and surrounding erythema and ecchymosis on her lower back (Figure 1). Multiple, painful, poorly-circumscribed subcutaneous nodules were noted on her inner thighs.

The patient's medical history included diabetes mellitus, hypertension, hypothyroidism, and psoriasis, as well as a documented allergy to penicillin. Patient denies any recent institution of new medications.

Two punch biopsies were obtained and formalin-fixed and paraffin-embedded in standard fashion (Figure 2). Analysis of both hematoxylin-eosin stained slides revealed a normal epidermis; however, vessel lumens within the deep reticular dermis and subcutaneous tissue demonstrated several occlusive, needle-shaped clefts with variable surrounding fat necrosis. These findings were consistent with the diagnosis of cholesterol embolization syndrome.

Shortly after the patient's initial office visit, laboratory data revealed elevations of both her blood urea nitrogen (BUN) and creatinine levels, indicative of acute renal failure. Patient underwent a brief hospital stay for temporary dialysis and management of her electrolyte imbalances and was discharged in stable condition. At follow-up several months later, patient was clear of any new lesions, and laboratory values were all within normal limits.

Discussion

Cholesterol embolization syndrome (CES) represents a disseminated atherosclerotic disease phenomenon initially described by Panum in 1862. According to some small case studies, its incidence is estimated at 6.2 per million and most commonly affecting Caucasian males at an average age of 66. Some authorities believe that the true incidence of CES is grossly underestimated, largely due to the high prevalence of subclinical disease or misdiagnosis. Thurlbeck and Castleman examined autopsies of hypertensive patients who had undergone aortic surgery, specifically focusing on the incidence of renal athereemboli. Although 70% of the test group demonstrated evidence of kidney involvement, approximately 30% of the age-and-sex-matched control group also demonstrated subclinical renal emboli. Risk factors for the development of CES include vascular procedures such as angioplasties and arteriograms, thrombolytic/anticoagulant therapies and other hyperlipidemic disease processes. Spontaneous occurrences may also arise in the setting of hypertension, secondary to the shearing forces of turbulent blood flow. Time to onset of cutaneous symptoms is quite variable and is predicated on the inciting event. For example, vascular procedures and thrombolytic intervention act to physically destabilize the atheromatous plaque, causing clinical manifestations often within days to weeks. Conversely, initiation of anticoagulant therapies inhibits the fibrin/coagulation cascade and typically has a more insidious onset over weeks to months. As stated previously, the pathophysiology of CES is due to the disruption of an established thrombus, with showering of microemboli into the systemic circulation. This cascade leads to tissue hypoxia, inflammatory response, and end-organ damage, namely the gastrointestinal tract, lungs, and kidneys. Interestingly, Franks and colleagues demonstrated that adenosine, a by-product of tissue ischemia and a potent vasodilator, actually decreases glomerular filtration and leads to incipient renal failure, a significant cause of morbidity/mortality in this population.

In a large case study by Falanga and colleagues, cutaneous manifestations of CES were found in 35% of patients. It was...
determined that livedo reticularis (49%) was the most frequent presenting sign, followed by gangrene (35%), acral cyanosis or the "blue toe syndrome" (28%), ulceration (17%), nodules (10%) and purpura (9%). Cutaneous symptoms are typically bilateral and typically affect the lower extremities, although unilateral variants have been reported. In the appropriate clinical setting, the constellation of extremity pain and livedo reticularis in the presence of palpable pulses is considered by some to be pathognomonic for CES. In our patient, catheterization of her superior mesenteric artery may have resulted in embolization of an intercostal artery, causing her lumbar ulceration, a rare and infrequently reported finding.

Because the clinical findings overlap and mimic a variety of dermatologic entities, further laboratory studies are often needed to confirm the diagnosis. Albeit non-specific, complete blood count (CBC) with differential, BUN/creatinine, urinalysis, erythrocyte sedimentation rate and creatine phosphokinase are markers that reflect a systemic inflammatory response and end-organ damage. Additional labs, including anti-neutrophilic cytoplasmic antibodies (ANCA), cryoglobulins, and hepatic screening panel, may be helpful to rule out other entities in the differential, including polyarteritis nodosa and other vasculitides. Systemic radiographic evaluation to identify the source of emboli is also of critical importance.

Many consider the histopathologic findings to be diagnostic for this condition. Biopsy reveals multiple biconvex, needle-shaped clefts within arteries and arterioles, which are remnants of cholesterol washed out during processing. Typically, vasculitis is not a histopathologic feature of CES, though acute and chronic inflammatory infiltrates have been demonstrated. Hyperplastic intimal proliferation is thought to be an additional late finding, and older lesions may show a foreign-body reaction. However, serial sections are often required to identify the segment involved. Incidental findings of cholesterol clefts in the absence of cutaneous disease have been reported, requiring clinicopathologic correlation.

Surgical intervention remains the gold standard for therapy of CES in an attempt to preserve functional tissue. However, poor surgical candidates require medical management. Anecdotal reports of IV iloprost, a prostacyclin analogue, have shown vasodilatory and anti-platelet properties. Similarly, statins have been suggested to possess plaque-stabilization attributes. Pentoxifylline and corticosteroids have also been used to reduce inflammation and pain, with inconsistent results. In all of these patients, supportive care, including the correction of fluid and electrolyte imbalances, is crucial.

Despite early detection and institution of proper therapy, CES continues to have a poor prognosis. Patients frequently have recurrent embolization, and amputation rates range between 15% and 32%. Mortality rates have been quoted as high as 81%, often secondary to declining cardiac and renal function.

In summary, CES remains a diagnostic and therapeutic challenge, often requiring a multidisciplinary approach. Fortunately, our patient received prompt supportive care and temporary dialysis, with complete resolution of her symptoms. Her favorable clinical course re-emphasizes the need for a high level of suspicion and early intervention to avert potentially fatal outcomes.

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ABSTRACT

The epidermal nevus syndromes (ENS) are a group of congenital disorders characterized by the association of epidermal nevi with abnormalities of the skin, eyes, skeletal, central nervous, cardiovascular, and genitourinary systems, as well as with malignant conditions. Because of the wide spectrum of organ involvement, a multidisciplinary approach is advisable in the management of these cases. These conditions rarely present a diagnostic difficulty, but the epidermal nevi are particularly difficult to treat and patients require continued medical care for associated abnormalities. As an illustrative case, we describe a 23-year-old woman with a systematized epidermal nevus, nevus sebaceus of the scalp and unilateral palmoplantar keratoderma with associated musculoskeletal defects. Her epidermal nevus has been relatively recalcitrant to treatment, and herein, a summary of the literature discussing the classification and management of epidermal nevi is presented.

Case Report

A 23-year-old female presented with extensive verrucous and hyperkeratotic lesions of the head and neck, trunk, genitalia and extremities. The lesions appeared focally on the chin at 6 months of age and slowly progressed in size, darkened color and distribution through adolescence. There was no history of erythroderma, vesicles, seizures or afflicted family members. A computed tomography scan of the brain was unremarkable. Past medical history includes early development of secondary sex characteristics, short stature and scoliosis. The lesions are largely asymptomatic, except for occasional pruritus and discomfort associated with the lesions in the anogenital and flexural areas. The patient is severely burdened by the cosmetic impairment caused by the lesions.

Physical examination revealed an obese female of short stature with normal intellect. Dermatologic examination revealed numerous flesh colored to brown, verrucous, discrete and confluent papules arranged in grouped, linear and whorled pattern, following the lines of Blaschko on the head and neck, torso, genitalia and extremities. [Fig. 1,2,3] Brachydactyly and clinodactyly were noted on several fingers, along with hyperkeratosis and keratoderma with transgrediens of the right palm and sole. [Fig. 4] A 15 cm alopecic, yellow-orange, verrucous plaque was present on the right parietal/superior aspect of scalp. [Fig. 5] Examination of the teeth, oral mucosa and nails was unremarkable.

Histologically, a shave biopsy of a verrucous papule taken from the right inguinal region showed features of a polypoid lesion with hyperkeratosis, papilomatosis and irregular acanthosis of the epidermis overlying a hyperplastic fibrous stroma with an absence of adnexal structures. Higher magnification reveals focal spongiosis and moderate mixed cell infiltrate in the papillary dermis. There was no evidence of acantholysis, dyskeratosis or epidermolytic hyperkeratosis. These features are non-specific, essentially that of a benign papilloma, but support a diagnosis of an epidermal nevus.[Fig. 6] A shave biopsy taken from the large alopecic plaque on the scalp showed the features of hyperkeratosis, papilomatosis, and irregular acanthosis of the epidermis. In the dermis there were increased numbers of mature sebaceous glands and small hair follicles and buds of basaloid cells, which may represent malformed hair germs. These features are consistent with a diagnosis of a nevus sebaceus (of Jadassohn). [Fig. 7]

To further evaluate the patient, the following studies were requested: chest/skeletal radiographs, computed tomography scan(brain), abdominal ultrasound, cardiac echocardiogram, ophthalmologic and neurologic consultation and complete metabolic profile. The patient was not able to complete this evaluation due to financial constraints.

Treatment with isotretinoin at age 8 for one year’s duration did not improve the appearance or halt the progression of the lesions. Carbon dioxide (CO2) laser treatment of the plantar surface of the feet, axillae and inner thighs did not produce significant clearing of the lesions and left minor scarring. Additionally, treatment has included local surgical deplaning and scissor excision of large or symptomatic
lesions, as well as cryotherapy to small or individual lesions. The patient is applying topical emollients to the skin daily and is using a topical 40% urea cream to her palms and soles. Consideration is being given for future treatment of selected areas with topical retinoids, 5-fluorouracil, dermabrasion and CO2 laser, each as monotherapy or in combination. She continues to be followed at regular intervals for surveillance.

Discussion

Epidermal nevi are benign hamartomas that result from hyperplasia of the epidermis and/or adnexal structures in a localized area of skin as a result of somatic mutations or genetic mosaicism. Epidermal nevi may be keratinocytic, follicular, sebaceous, apocrine, or eccrine in origin arising from the pluripotent cells of the embryonic ectoderm. These nevi may be further classified into a number of distinct variants, which are based on clinical morphology, extent of involvement, and the predominant epidermal structure in the lesion. Variants include keratinocytic nevi, also called verrucous or linear epidermal nevi, and organoid nevi, such as, nevus sebaceous, nevus comedonicus, eccrine nevus, apocrine nevus, Becker's nevus and white sponge nevus. Keratinocytic nevi are the most common of the epidermal nevi.

The incidence of all types of epidermal nevi is estimated to be 1 in 1000 live births, equally affecting males and females. Most cases arise sporadically during embryonic development, but familial patterns of inheritance have been observed for certain types of epidermal nevi.

The majority of epidermal nevi appear at birth or within the first year of life, however, they may also develop later during childhood or adulthood. Clinically, verrucous epidermal nevi are characterized by verrucous papules often coalescing into well-demarcated plaques. They may be skin-colored, brown, or gray-brown. The linear arrangement of verrucous epidermal nevi typically follows the lines of Blaschko, reflecting the pattern of stem cell migration during embryonic development. The distribution, surface characteristics, and histology of the lesions are variable. Histologically, verrucous epidermal nevi show features of hyperkeratosis, focal parakeratosis, acanthosis, and dermal smooth muscle hyperplasia. The epidermal nevi show features of hyperkeratosis, acanthosis, and papillomatosis. Epidermolysis may be noted histologically in diffuse cases, and less commonly, in localized epidermal nevi. Paller et al. identified a familial pattern of disease, in which patients with large or systematized verrucous epidermal nevi had an

<table>
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<th>Table I. Summary of the epidermal nevus syndromes*</th>
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Patients with large or widespread epidermal nevi and those with ENS, require a careful history with particular attention given to developmental history, attainment of milestones, history of seizures, and abnormalities of the bones, eyes, and urinary tract. Thorough mucocutaneous, neurologic, ophthalmologic, and orthopedic examinations are necessary, with special attention paid to examination of the eyes, head circumference, spine, extremities, and central and peripheral nervous systems. Consultations with pediatric, ophthalmologic, neurologic, and orthopedic services should be considered. Depending on the findings on history and physical examination, further investigations may be indicated. Establishing the diagnosis and screening for associated abnormalities may involve skin biopsies, blood chemistry, chest and skeletal radiographs, urinalysis, electroencephalograms, computed tomography scans or magnetic resonance imaging, echocardiography, abdominal ultrasonography, and serum and urine measurements of calcium and phosphorus metabolism. A regular follow-up program should be established for routine monitoring and surveillance because of the risk of primary and secondary tumors of the skin and viscera, both benign and malignant.

Because the skin lesions only rarely become malignant, supported by observations of basal cell carcinoma arising within a nevus sebaceous, the indication to treat is most often for cosmetic improvement. Hence, the removal of these lesions is performed for the purpose of reducing disfigurement and alleviating discomfort. Localization to cosmetically sensitive areas, such as the head and neck or distal extremities, can be very embarrassing and distressing for patients. Extensive epidermal nevi can cover much of the body surface and, if present in intertriginous areas, can become tender, macerated plaques and a potential source of infection.

The treatment of epidermal nevi is challenging. Epidermal nevi have been notoriously difficult to treat due to their large size and occasional conspicuous location. Multiple medical and surgical treatments for epidermal nevi have been attempted, but no ideal or universally acceptable treatment has emerged. The treatment of choice for small epidermal nevi is excision. Lesions may enlarge slowly in childhood, become darker and thicker, and by adolescence reach a stable size after which further growth is unlikely. Therefore, it is preferable to delay surgery until the lesions have clinically reached final maturation. Early excision may result in recurrence.

Many medical treatments for epidermal nevi have been attempted. Corticosteroids applied under occlusion or by injection, as well as tretinoin cream applied topically, may sometimes be partially effective. Systemic retinoids may be beneficial for the treatment of widespread systematized epidermal nevi, but the requirement of life-long therapy may be inappropriate for smaller lesions. Retinoids, both systemic and topical, may be most effective in lesions with histologic features of epidermolytic hyperkeratosis. Nelson et al. have previously discussed the therapeutic rationale behind retinoid therapy of epidermal nevi. They described successful management of one patient using a combination treatment of 0.1% tretinoin cream twice daily and 5% 5-FU once daily for 6 months. No occlusion was used and recurrence was noted 3 to 4 weeks after cessation of treatment. However, continuing the topical combination 2 to 3 times a month was effective as maintenance therapy. In one report, a patient with nevus comedonicus who failed multiple topical and systemic therapies was successfully treated with 12% ammonium lactate lotion applied twice daily.

The treatment of linear verrucous epidermal nevus (LVEN) has also proven difficult. A review by Fox and Lapins describes various approaches to treating verrucous epidermal nevi using intralesional steroids, topical steroids with and without occlusion, dithranol, phenol peeling, topical tretinoin under occlusion, podophyllin ointment under occlusion, 5-FU under occlusion, dermabrasion, and cryotherapy. They found the surgical modalities were most effective at clearing the lesions, but resulted in significant scarring. Other agents used to treat LVEN have since been reported, including a successful response with isotretinoin and anthralin. Moreover, topical calcipotriol has been reported to be beneficial in treating the inflammatory variant of LVEN, which has been argued to represent true linear psoriasis or superimposed psoriasis. The literature is replete with case reports and anecdotal evidence of successful treatment with various agents, but there have been only a few large series of patients in randomized studies.

Removal of lesions is often technically difficult. Superficial means of removal frequently result in recurrence. Aggressive approaches may be more successful, but also carry a higher risk of postoperative scarring. Surgical excision, dermabrasion, cryosurgery, electrosurgery, and laser surgery have each been used to treat epidermal nevi. In particular, surgical excision always causes scar formation and thus is reserved for the smallest lesions. Dermabrasion, if superficial, is associated with a high rate of recurrence, and deep dermal dermabrasion can result in hypertrophic scarring. Cryosurgery has similar limitations, with the risks including slow healing, exudation, swelling, and not uncommonly, depigmentation.

Physicians have been performing laser
treatment on epidermal nevi for decades.13 Recent advances in laser technology have increased the ease, precision, and safety of such treatments. Several reliable and effective methods for treating epidermal nevi with lasers have been developed. Several articles in the literature detail such treatments. Different types of lasers have been reported to be effective. Successful eradication appears dependent on the clinical characteristics of the nevus. Softer, flat nevi were more responsive to the argon laser and carbon dioxide laser than were the harder, keratotic forms of LVEN.13,29 The pulsed ruby laser effectively lightened dark-colored epidermal nevi, but its efficacy has not been shown in nonpigmented nevi.31 Long-pulsed ruby lasers have been used10 with 1 to 4 treatments resulting in good cosmetic improvement. The handful of patients treated did not experience lesion recurrence during 2 to 3 years of follow up. Hypopigmentation, either transient or permanent, was noted in some cases, as was decrease in hair growth at the treated sites.

Additionally, other lasers have been used to treat epidermal nevi. Targeted vascular lasers for the treatment of inflammatory linear verrucous epidermal nevus (ILVEN)32 has been reported to be effective. In one report, the 585 nm flashlamp-pumped pulsed dye laser was successful at relieving pruritus, but resulted in only partial clearing of the lesion.29 Erbium:YAG lasers have been used to permit more precise removal of epidermal nevi tissue, but difficulty in achieving hemostasis with these devices can make treatment impractical.13,34 In deeper lesions, bleeding can complicate the procedure, and scar formation may occur. Newer modified erbium lasers have greater coagulative capacity and may be used in a manner similar to that for the pulsed carbon dioxide laser. Continuous-wave carbon dioxide laser treatment of epidermal nevi was reported by Ratz, Bailin and Wheeland,15 treating 15 patients over a period of 5 years. Since then, others have noted success with this approach. Hohenleutner et al29 found the continuous-wave carbon dioxide laser able to remove epidermal nevi of various types and textures. “Soft, flat, papillomatous” variants were treated without scar formation even when they covered substantial body surfaces, and “hard, keratotic” lesions responded but with a tendency to hypertrophic scar formation.13,30 They speculated that removal of the firmer lesions may require greater depth of ablation of the dermis and hence increased risk of damage to adnexal structures. The pulsed carbon dioxide laser has several advantages over continuous-wave devices. Target lesions can be flattened in a manner that permits precise control of depth of ablation. Each laser pass vaporizes a limited amount of tissue, and a series of such thin slices can be removed to reach the desired end point. Extremely thick lesions can be debulked with electrocautery or the laser on continuous wave mode, and the setting can be changed to pulsed mode once the epidermal component is mostly removed.33 However, a limitation of this technique is its slowness. Numerous laser passes to the same area are time-consuming, and extensive lesions covering large parts of the body are not amenable to such treatment. Also, recurrences can occur months or years after removal of epidermal nevi by any method. Patients should be made aware of this, as well as the possibility of hypertrophic scar formation.

In summary, the diagnosis of epidermal nevi can usually be made on the clinical appearance and distribution of the lesions alone. In the context of ENS, a skin biopsy will not only confirm the diagnosis, but may also determine the predominant cell type, presence of inflammation, depth of lesion and characteristics of keratinocytes (ie. acantholysis, dysplasia, epidermolytic hyperkeratosis) which may have implications in the prognosis and selection of appropriate therapies. Excision should be reserved for smaller nevi or lesions, such as nevus sebaceous, which carry a low risk of malignant transformation. The treatment of extensive epidermal nevi should generally be approached with a combination of medical and surgical methods. The management of patients with ENS requires an interdisciplinary team approach because of the multiple organ systems involved. Furthermore, the treatment of epidermal nevi in this setting should be guided by the patient’s cosmetic desires and need for symptomatic relief. Realistic expectations should be established and long-term follow up is necessary because of the potential for multisystem involvement and the overall increased risk of malignancy.

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Observational Case Report: Acanthosis Nigricans Regression with Rosiglitazone after Previous Treatment with Pioglitazone

Derrick Adams, Captain, D.O., USAF, MC

ABSTRACT

After an institutional decision to delete pioglitazone from formulary and add rosiglitazone, near complete resolution of acanthosis nigricans was observed in three obese African American type 2 diabetics. This case report details the clinical presentations of the lesions and medical history of the patients.

Acanthosis nigricans (AN) is a non-specific, cutaneous pattern that may accompany obesity, diabetes, internal malignancies, pineal tumors, multiple endocrinological abnormalities, and use of nicotinic acid. AN is a clinically significant lesion that may predict the early onset of insulin-resistance syndromes or diabetes. The roles of insulin and insulin-like growth factor on keratinocytes are well-recognized in the pathogenesis of this epidermal hyperplasia. AN is classified as either malignant or benign, the latter including obesity-related, hereditary and endocrine syndromes. Although the lesions range in severity of involvement, all are characterized by brownish thickening that is often described as warty or leathery. Common areas of involvement are the flexural surfaces of the neck, axillae, groin and dorsal surfaces of fingers, although lesions can appear anywhere, including the oral cavity. Lesions are usually asymptomatic and require no treatment. Retinoids, 12% lactic acid cream, oral isotretinoin and topical cholecalciferol are effective for reducing lesions in areas of maceration or for cosmetic appearances.

Three well-controlled African American type 2 diabetics managed on pioglitazone (Actos®, Takeda Chemical Industries, Ltd) and metformin were transitioned to rosiglitazone (Avandia®, GlaxoSmithKline) and continued on their previous metformin doses. The decision to alter the patients' course of therapy was based solely upon financial decisions made at the institutional level, as none were experiencing any side effects or complications of pioglitazone therapy. Each patient reported that the typical acanthotic lesions had been present since young adulthood (the patients' ages were 46, 44, and 69 years old). Only one of the three patients had sought therapy for the asymptomatic lesions and had received Retin-A 0.025% cream from a dermatologist. This patient chose to discontinue use after one month secondary to financial issues. The diagnosis of AN was annotated in each patient's chart at least once within the previous four years by either a family practice physician or dermatologist.

Upon physical examination, two of the patients demonstrated only trace papillomatous hyperpigmentation to the dorsal neck surfaces. Comparison through previous documentation revealed quite extensive involvement of not only the dorsal neck but also of bilateral axillae in these individuals. The third patient was free of any lesions at the time of examination, but her chart had noted right axillary involvement and right peri-areolar lesions.

Clinical measurements and laboratory values of the three individuals changed minimally after treatment was implemented with rosiglitazone. The average BMI prior to the transition was 34 and was unchanged when the lesions were first noted to be absent. The hemoglobin A1c was noted to have increased an average of 0.35%, which was of no clinical significance. Blood pressures, liver function tests, creatine, and urine microalbumin measurements were essentially unchanged throughout the stated period (although one patient was changed from an angiotensin-receptor blocker to an angiotensin-converting enzyme inhibitor). Collectively, there was no history of internal malignancy or polycystic ovarian syndrome. The average dose of the three patients was 5.3 mg and the average length of rosiglitazone treatment was 11 months when regression was first documented.

This clinical observation suggests that rosiglitazone may play a role in the treatment of AN. There are three separate, documented case reports on improvement of AN with metformin, but there have been no literature reports addressing the use of thiazolidinedione antidiabetic agents. The mechanism of action of both metformin and rosiglitazone remain only partially elucidated; however, it is reasonable to hypothesize that they may share similar effects on keratinocytes and the complex regulations leading to AN formation. It is unclear why these particular patients had regression of their AN lesions with rosiglitazone and not pioglitazone. This observation has led to a proposal for further study that is currently before the facility's Internal Review Board.
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