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Well things do just keep getting better! This is our fourth issue of the JAOCD. Each issue has gotten better and more informative. As a member of the AOCD, you should take great pride in our publication.

We have more residents in our programs then ever. The Education Evaluation Committee (EEC) has made it mandatory for each resident to submit their annual paper for publication to a medical journal. The residents have had the requirement to write one paper each year of their residency that is suitable for publication. It will require a very small effort on the resident’s behalf to take the next step and submit their manuscript for consideration for publication.

As the editors of the JAOCD, we hope that the residents will consider the JAOCD when the time comes for them to submit their annual papers. They will see that it is a relatively easy process and it is our hope that they will be encouraged to submit other papers throughout their three years of residency.

We continue to strive for improvement and growth in every aspect of our journal. We continue to strive for the next milestone and be able to publish the JAOCD four times a year. Again, when this happens, we will be able to have our journal listed in the Library of Congress as well as have it listed in Index Medicus.

We will continue to solicit your contribution in the way of presenting an interesting case or even a pearl on office management. We require consistency. Consider becoming a consistent contributor, always looking out for what would be interesting to the readers of our journal.

We extend our sincere appreciation for continued support to our Founding Sponsors. Our deepest thank you goes to Allergan Skin Care, Connetics Corporation, Global Pathology Laboratory Services, Novartis Pharmaceuticals Corporation, Medicis-The Dermatology Company and 3M Pharmaceuticals who have made the financial commitment to 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. (Associate Editor)
At the first sign of...

In patients with recurrent genital herpes or herpes zoster
Pregnancy

Two placebo-controlled studies in a total of 130 otherwise healthy men with a normal sperm profile over an 8-week baseline period and recurrent genital herpes receiving oral Famvir (250 mg b.i.d.) (n=66) or placebo (n=64) therapy for 18 weeks showed no evidence of significant effects on sperm count, motility or morphology during treatment or during an 8-week follow-up period.

Geriatics

Of 816 patients with herpes zoster in clinical studies who were treated with Famvir, 248 (30.4%) were ≥65 years of age and 163 (19.9%) were ≥75 years of age. No overall differences were observed in the incidence or types of adverse events between younger and older patients.

ADVERSE REACTIONS

Immunocompetent Patients

The safety of Famvir® (famciclovir) has been evaluated in clinical studies involving 816 Famvir-treated patients with herpes zoster (Famvir, 250 mg b.i.d. to 750 mg t.i.d.); 528 Famvir-treated patients with recurrent genital herpes (Famvir, 125 mg b.i.d. to 500 mg b.i.d.); and 1,197 patients with recurrent genital herpes treated with Famvir as suppressive therapy (125 mg b.i.d. to 250 mg t.i.d.) of which 570 patients received Famvir (open-labeled and/or double-blind) for at least 10 months.

CONTRAINdications

Famvir® (famciclovir) is contraindicated in patients with known hypersensitivity to the product, its components, and Dacovir® (penciclovir) cream.

PREcautions

General

The efficacy of Famvir® (famciclovir) has not been established for initial episode genital herpes infection, ophthalmic zoster, disseminated zoster or in immunocompromised patients with herpes zoster.

Dosage adjustment is recommended when administering Famvir to patients with creatinine clearance values <60 mL/min. (See DOSAGE AND ADMINISTRATION in the full prescribing information) in patients with underlying renal disease who have received inappropriately high doses of Famvir for their level of renal function, acute renal failure has been reported.

Information for Patients

Patients should be informed that Famvir is not a cure for genital herpes. There are no data evaluating whether Famvir will prevent transmission of infection to others. As genital herpes is a sexually transmitted disease, patients should avoid contact with lesions or intercourse when lesions and/or symptoms are present to avoid infecting partners. Genital herpes can also be transmitted in the absence of symptoms through asymptomatic viral shedding. If medical management of recurrent episodes is indicated, patients should be advised to initiate therapy at the first sign or symptom.

Drug Interactions

Concurrent use with probenecid or other drugs significantly eliminated by active renal tubular secretion may result in increased plasma concentrations of penciclovir.

The conversion of 6-oxo-penciclovir to penciclovir is catalyzed by aldehyde oxidase. Interactions with other drugs metabolized by this enzyme could potentially occur.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Famciclovir was administered orally unless otherwise stated.

Carcinogenesis: Two-year dietary carcinogenicity studies with famciclovir were conducted in rats and mice. An increase in the incidence of mammary adenocarcinomas (a common tumor in animals of this strain) was seen in female rats receiving the high dose of 600 mg/kg/day (1.5 to 9.0 x the human systemic exposure at the recommended daily oral doses of 500 mg t.i.d.; 250 mg b.i.d., or 125 mg b.i.d. based on area under the plasma concentration curve comparisons (24 hr AUC) for penciclovir). No increases in tumor incidence were reported in male rats treated at doses up to 240 mg/kg/day (0.9 to 5.4 x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.4 to 2.4 x the human AUC).

Mutagenesis: Famciclovir and penciclovir (the active metabolite of famciclovir) were tested for genotoxic potential in a battery of in vitro and in vivo assays. Famciclovir and penciclovir were negative in in vitro tests for gene mutations in bacteria (S. typhimurium and E. coli) and unchallenged DNA synthesis in mammalian Hela-S3 cells (at doses up to 10,000 and 5,000 mcg/mg, respectively). Famciclovir was also negative in the L5178Y mouse lymphoma assay (5000 mcg/ml), the in vivo mouse micronucleus test (4800 mcg/ml), and rat dominant lethal study (5000 mcg/kg). Famciclovir-induced increases in polyplody in human lymphocytes in vitro and the absence of chromosomal damage (1200 mcg/ml). Penciclovir was positive in the L5178Y mouse lymphoma assay for gene mutation/chromosomal aberrations, and with and without metabolic activation (1000 mcg/ml). In human lymphocytes, penciclovir caused chromosomal aberrations in the absence of metabolic activation (250 mcg/ml). Penciclovir caused an increased incidence of micronuclei in mouse bone marrow in vivo when administered intravenously at doses highly toxic to bone marrow (500 mg/kg), but not when administered orally.

Impairment of Fertility: Testicular toxicity was observed in rats, mice, and dogs following repeated administration of famciclovir or penciclovir. Testicular changes included atrophy of the seminiferous tubules, reduction in sperm count, and/or increased incidence of sperm with abnormal morphology or reduced motility. The degree of toxicity to male reproduction was related to dose and duration of exposure. In male rats, decreased fertility was observed in male rats treated at doses up to 240 mg/kg/day (0.9 to 5.4 x the human AUC), or in male and female mice at doses up to 600 mg/kg/day (0.4 to 2.4 x the human AUC).

Changes in seminal plasma were reported at all dosages examined in the rat, but were not significantly different from controls. No effects on specific semen parameters were observed in dogs or in any of the primate studies.

Carcinogenicity, Mutagenesis, Impairment of Fertility: To monitor maternal-fetal outcomes of pregnant women exposed to Famvir, Novartis Pharmaceuticals Corporation maintains a Famvir Pregnancy Registry. Physicians are encouraged to register their patients by calling (888) 669-6682.

Pharmaceuticals Corporation maintains a Famvir Pregnancy Registry. Physicians are encouraged to register their patients by calling (888) 669-6682.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.

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Barcelona, Spain

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Nursing Mothers

Followling oral administration of famciclovir to lactating rats, penciclovir was excreted in breast milk at concentra-

tions higher than those seen in the plasma. It is not known whether it is excreted in human milk. There are no data on the safety of Famvir in infants.

Usage in Children

Safety and efficacy in children under the age of 18 years have not been established.
In Recurrent Genital Herpes

**FAMVIR®** stops pain and burning in a median of 2 days or less with episodic therapy\(^1\)\(^1\)

- Median time (days) to cessation vs placebo (pain: 2.0 vs 2.4, \(P<.006\); burning: 1.7 vs 2.1, \(P<.001\))

**FAMVIR keeps patients outbreak-free for nearly a year with suppressive therapy\(^2\)\(^,3\)**

- Median time to first recurrence was 336 days with FAMVIR vs 47 days with placebo (\(P<.001\))\(^1\)
- The safety and efficacy of FAMVIR for suppressive therapy have not been established beyond 1 year

In Herpes Zoster

**Only FAMVIR is proven to shorten the median duration of PHN by 100 days vs placebo\(^4\)\(^,5\)**

- For patients \(\geq 50\) years

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome Measure</th>
<th>FAMVIR</th>
<th>Placebo</th>
<th>(P) Value</th>
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<tbody>
<tr>
<td><strong>In Recurrent Genital Herpes</strong></td>
<td>Median time to cessation vs placebo (pain: 2.0 vs 2.4, (P&lt;.006); burning: 1.7 vs 2.1, (P&lt;.001))</td>
<td><strong>FAMVIR</strong></td>
<td><strong>Placebo</strong></td>
<td>(P&lt;.006)</td>
</tr>
</tbody>
</table>

\(^{1}\) Therapy should be initiated as soon as herpes zoster is diagnosed. The efficacy of treatment started more than 72 hours after rash onset has not been established.

\(^{2}\) No significant difference in overall incidence of PHN for famciclovir vs placebo. In patients <50 years, no statistically significant difference seen in duration of PHN.

\(^{3}\) The efficacy of FAMVIR has not been established for initial-episode genital herpes infection, ophthalmic zoster, disseminated zoster, or in immunocompromised patients with herpes zoster.

\(^{4}\) Therapy started as soon as herpes zoster is diagnosed. The efficacy of treatment started more than 72 hours after rash onset has not been established.
The AOCD has seen a tremendous growth over the past few years, with the number of resident’s almost doubling and an increased membership in the organization. Because of this unprecedented growth, the Executive Committee has decided to bring on a Director of Development, in order to expand the relationships it has with its current corporate partners, as well as to cultivate and develop relationships with new partners.

The Foundation for Osteopathic Dermatology (FOD) was also formed in order to raise awareness and provide the public with necessary health information, and to support research through grants and awards.

The AOCD strives for the creative delivery of highly sophisticated education and training programs. Contributions that are made, allow the AOCD to grow these opportunities, as well as to operate the organization. This is an ambitious goal, and will require the combined efforts of every member, and every component of the organization.

Consistent commitment will allow the AOCD to be well positioned to serve its members and to continue to enhance patient care.

I am enjoying the opportunity of serving this well respected organization, and fulfilling its commitment to its members, who represent all facets in the field of dermatology, and at all stages of their professional career.

I will be in contact with all members throughout this year, and I look forward to serving your organization and working with you to advance the AOCD.

Please feel free to contact me.

Respectfully,
Shirley Gottlieb
Director of Development
954-963-5862 (office)
954-232-2025 (cell)
954-985-3934 (fax)
shirleygottlieb@aol.com
Introduction:

EB is a mechanobullous disease that predominantly affects skin and mucous membranes. The key clinical feature is increased fragility of the skin, which manifests as blisters and erosions secondary to minor trauma. This is due to genetic aberrations at the level of the cutaneous basement membrane zone (BMZ). Diagnosis of the condition is by detailed history, clinical features, transmission electron microscopy (TEM), immunofluorescence antigen mapping and immunohistochemical staining with EB specific monoclonal antibodies.1

Case Report:

A full-term baby boy was born to a 22-year old primigravida through normal spontaneous vaginal delivery. At the time of the delivery, the baby was jaundiced (total bilirubin 3.7 mg/dl; normal 0.1-1.0) meconium stained and weighing 3.17 kilograms with apgar score 7 at the seventh minute. In addition he was having large bullous lesions on the back and feet dorsa. Some of the lesions were ruptured with denuded ulcerated areas. Apart from that his vital signs, systemic examination, oral mucosa, nails and hair were within normal limit. Family history was negative for any genetic disorder. Basic laboratory evaluation including complete blood count, serum electrolytes, liver and renal function tests, stool and urine analysis were normal.

During the first 24 hours the neonate developed seizure for which he was started on phenobarbital, ampicillin and cephalosporin because of suspected sepsis. On the second day, the neonatologist consulted us for his skin lesions. Full cutaneous evaluation revealed ulcerated areas on the back, upper and lower limbs and oral mucosa (figure 1,2). No intact blisters were seen. So our preliminary diagnosis was inherited form of EB. Two skin punch biopsies were taken from the edge of intact newly formed blisters on the left foot and arm for light microscopy, immunofluorescence and transmission electron microscopy. Histological evaluation revealed cleavage at the dermoepidermal junction with normal epidermal and dermal constituents. Immunofluorescence for IgM, IgA, IgG, C3 and fibrinogen was negative while for antigen type IV collagen, laminin and bullous pemphigoid were not done due unavailability of the reagents.

Transmission electron microscopy revealed basal cells were present with continuous basal lamina and a cleavage plane localized below the lamina densa that lines the blister roof (figure 3). Comment on the anchoring fibrils could not be specified due to specimen quality. A diagnosis of recessive dystrophic EB of Hallopeau-Siemens type was entertaine. A strict management plan was undertaken.

During the first week of treatment, the neonate general condition was stable with no further seizures. No new blisters formed and the old blisters appeared to be healing with scarring. During the second week the infant had difficulty with oral feeding and he looked ill, although his vital signs were stable. Blood cultures and the skin surface culture demonstrated pseudomonas aeruginosa. The skin, mouth lesions, ears, and nose were also culture positive for pseudomonas aeruginosa.

Changes to the antibiotic protocol were based on the antibiotic sensitivity results. Unfortunately, the patient skin condition was worsening and nasogastric tube feeding was instiuted. By the end of the second week, the patient had cyanosis with oral and nasal bleeding. The vital signs deteriorated and a prolonged prothrombin and partial thromboplastin time with marked leucopenia were evident. Cardiopulmonary arrest ensued and the patient failed resuscitation efforts.

Discussion:

EB is a mechanobullous disease that predominantly affects the skin and mucous membranes. The prevalence rate of epidermolysis bullosa (EB) is estimated to be 19 per million in the United States. The prevalence rate of dystrophic epidermolysis (DEB) is estimated at 2.4 cases per million population.2 The diagnostic clinical feature in EB is increased fragility of the skin, which manifests as blisters and erosions secondary to minor trauma. However, there is considerable phenotypic
variability, and the presence of extracutaneous manifestations adds to the complexity of this disorder.1

In 1999, classification of inherited EB was revised based on commonly recognized forms and the associated genes involved.2 Table 1 lists the currently recognized types and subtypes of inherited EB. There are additional clinical phenotypes of DEB still recognized as subtypes in the revised classification system which include dominant DEB-pretrialbal, DEB-transient bullos dermolysis of the newborn, dominant DEB-pruriginosa, recessive DEB-inversa, recessive DEB-centripetalis and DEB, autosomal dominant/autosomal recessive heterozygote.3

Physiologically, the basement membrane zone (BMZ) is important for stable association of the epidermis to the underlying dermis and it consists of hemidesmosomes, anchoring filaments, and anchoring fibrils that form an interconnecting network extending from the intracellular milieu of basal keratinocytes across the dermoepidermal basement membrane to the underlying dermis. Any aberrations in this network can lead to increased fragility of the skin at the level of the BMZ. Genetically a large number of mutations linked to type VII collagen gene (COL7A1) located at 3p21.1 in both recessive (RDEB) and dominant forms of DEB (DDEB).4,5,6 Clinically most patients with DEB have a relatively mild dominantly inherited disease and only a minority suffer from severe recessive subtypes. In Dominant Dystrophic Epidermolysis Bullosa (DDEB) the clinical spectrum ranges from a milder phenotype, manifested by localized blistering at sites of maximal trauma to generalized blisters that subsequently heal with scarring. The age of onset is early childhood. The nails of both upper and lower extremities tend to be abnormal with no extracutaneous manifestations.7 An uncommon variant of dystrophic EB called transient bullous dermolysis of the newborn presents with blistering at sites of trauma that heals after several months without scarring.8 In Recessive Dystrophic Epidermolysis Bullosa of Hallopeau-Siemens Subtype (RDEB-HS), patients have exceedingly fragile skin that blisters at birth. It is extremely pruritic and painful and mucosal blisters usually occur. Extensive scarring may lead to contrac-
tures or fusions of digital web spaces (pseudosyndactyly). The oral cavity and esophagus may become severely involved with subsequent development of microstomia, obliteration of oral vestibule, and ankylglossia. Enamel hypoplasia and cementum disorders may also occur. A devastating complication unique to patients with RDEB, is the increased propensity for squamous cell carcinoma of the skin.9

In Recessive Dystrophic Epidermolysis of Non–Hallopeau–Siemens Subtype (RDEB-nHS) patients lack the cutaneous and extracutaneous features characteristic of the Hallopeau–Siemens subtype. In inverse RDEB, blisters are present at birth and later cutaneous lesions are localized almost exclusively in skin folds. Milia, atrophic scarring, scarring alopecia and nail dystrophy can be seen. In RDEB-centripetalis, lesions occur during infancy and have a progressive centripetal spread with no intra-oral or other extra-cutaneous involvement.10,11 Epidermolysis bullosa pruriginosa can be both autosomal dominant and recessive manifesting highly pruritic, violaceous, pretibial cutaneous nodules and plaques that may be confused with hypertrophic lichen planus and nodular prurigo.

The onset of skin lesions is variable and can occur as late as 10 years of age.11 Besides blistering in DEB, other skin disorders that may occur simultaneously include cutaneous neoplasms, eczema, atopic and allergic dermatitis.

Extra-cutaneous involvement may include the abnormality of the teeth, gastrointestinal tract, upper respiratory tract, genitourinary tract, eyes and cardiovascular system.12 Gastrointestinal manifestations include dysphagia, esophageal stricture, pyloric stenosis, anal stricture, chronic constipation and fecal impaction.13 Dental involvement may include gingival blisters or erosions, enamel hypoplasia, dental caries, malocclusion and premature loss of teeth.14 Tracheolaryngeal symptoms may include chronic hoarseness, inspiratory stridor and laryngeal stenosis or obstruction.15

Genitourinary involvement may include urethral meata stenosis, urinary retention, glomerulonephritis, nephrotic syndrome secondary to renal amyloidosis and menstrual abnormalities.16,17 Ocular findings range from corneal erosion, corneal scarring, symblepharon, blepharitis, ectropion, lacrimal duct obstruction and blindness.18 Otitis externa, external auditory canal stenosis, chronic otitis media and hearing loss have also been reported.19 Anemia and growth retardation attributed to iron deficiency and chronic disease are frequently seen. Common causes of death in DEB patients include squamous cell carcinoma, sepsis, pneumonia, respiratory failure, failure to thrive, renal failure, heart disease and stroke.1

Our patient presented with RDEB-HS type which was complicated with sepsis to which he succumbed. An early detailed history including mapping of the family pedigree is mandatory. An absence of other known affected family members does not establish the mode of transmission to be autosomal recessive. Spontaneous

Table 1: Classification of inherited Epidermolysis Bullosa (EB).

<table>
<thead>
<tr>
<th>Major types</th>
<th>Mode of inheritance</th>
<th>Major subtypes</th>
<th>Level of cleavage</th>
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<tbody>
<tr>
<td>EB simples</td>
<td>Autosomal dominant</td>
<td>EBS-Weber-Cockyne EBS-Kobner EBS-Dowling-Meara</td>
<td>Intraepidermal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EBS-Muscular dystrophy</td>
<td></td>
</tr>
<tr>
<td>Junctional EB</td>
<td>Autosomal recessive</td>
<td>JEB-Herlitz  JEB-Non-Herlitz  JEB-Pyloric atresia</td>
<td>Intralamina densa</td>
</tr>
<tr>
<td>Dystrophic EB</td>
<td>Autosomal dominant</td>
<td>Dominant DEB</td>
<td>Sublamina densa</td>
</tr>
<tr>
<td></td>
<td>Autosomal recessive</td>
<td>Recesive DEB-Hallopeau-Siemens</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recesive DEB-non-Hallopeau-Siemens</td>
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Figure 3 Transmission electron microscopy showing a cleavage plane localized below the lamina densa (LD) that lines the blister roof. LL, lamina lucida; BK, basal keratinocyte.
mutation or the incomplete penetration of an autosomal dominant trait could play a role.19

Non-molecular laboratory tests that may be helpful in establishing a diagnosis of EB include transmission electron microscopy (TEM), immunofluorescence antigen mapping and immunohistochemical staining with EB specific monoclonal antibodies. TEM remains the gold standard for it permits not only identification of the ultrastructural level of skin cleavage, but also the appearance of the specific structures such as keratin, tonofilaments, hemidesmosomes, sub-basal dense plates and anchoring fibrils.21 In DEB, TEM features include abnormal fibrils and blister formation beneath the lamina densa of the dermoepidermal junction. TEM demonstrated this feature in the case of our patient.22

The major disadvantages of TEM are technical difficulties and cost.1 Immunofluorescence antigen mapping involves a modified indirect immunofluorescence method using patient’s skin and antibodies against three known basement membrane antigens (bullous pemphigoid antigen-3, laminin 5 and type VII collagen. All three antibodies bind exclusively to the induced blisters’ roof.23 Prenatal diagnosis is important not only to identify fetal anomalies, but also to provide choices to parents at risk of having a child with EB which is done by obtaining samples of fetal skin at 17 to 21 weeks of gestation for light and electron microscopic examination and immunohistochemical evaluation. Features that suggest diagnosis of DEB include: dermoepidermal junction separation below the lamina densa where lamina densa forms the blister roof, absent or poorly developed anchoring fibrils, and reduced or absent expression of type VII collagen.1 DNA based test for first-trimester prenatal diagnosis using DNA from chorionic villi and amniotic fluid as early as 10 weeks of gestation is new method of making the diagnosis of EB. In embryos resulting from in vitro fertilization, preimplantation genetic diagnosis can be performed at the eighth cell stage before the embryo is implanted in the uterus.24 If the diagnosis reveals a normal or carrier genotype, the original blastocyst can be implanted into the uterus while the embryos that have an affected genotype are discarded.

Therapy for EBD should be directed toward prevention of skin trauma and avoiding new blister formation, prevention of secondary bacterial infection, aggressive treatment of infection when it occurs, measures to improve wound healing, maintenance of good nutrition, treatment of all correlative complications and, finally, rehabilitation.

Prevention of infection is achieved by changing dressings daily, applying topical antibiotics to lesions and nonstick dressings to denuded areas, and draining the blisters.1 Methylcellulose containing artificial tears are useful to prevent ocular abrasions.1 Stool softeners for management of chronic constipation.20 Oral prophylaxis with sulfasalazine prevents blister formation and provides comfort for mouth lesions.21 Non-healing areas of the skin can be treated with split-thickness skin grafts and careful use of hand splints help prevent development of mitten deformities.25

A nutritionist should be consulted about the nutritional needs of an infant with DEB. The caloric and nutritional requirements can be twice that of children without blistering disease.1 With possible future isolation of the corresponding normal alleles, gene therapy can become a potential cure for these conditions.26

Conclusion:

This is a case presentation and discussion of a severe case of RDEB of Hallopeau Siemens type with no known affected family member. Our patient’s condition was complicated by sepsis and eventual death. DEB is an aggressive disease process with severe potential complications. This case should help alert physicians to develop a strict and proper management plan. A multidisciplinary approach through cooperation of pediatricians, dermatologists and nutritionists can help these patients through their disease process.

References

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Familial Cylindromatosis: A Case Report

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* 2nd year resident, Department of Dermatology, University Hospitals Health System of Cleveland, Case Western Reserve University, Cleveland, Ohio; Department of Dermatology, Wade Park Veterans Administration, Cleveland, Ohio.

ABSTRACT

Cylindromas are benign adnexal tumors whose histogenesis is still controversial. The scalp is most frequently involved, but other areas of the body may be affected. The lesions are smooth, dome-shaped, and erythematous to blue nodules, often with prominent telangiectasias, which can be solitary or multiple. Solitary tumors are sporadic, while the multiple tumors are inherited in an autosomal dominant pattern. We present a case report and a review of the current understanding of familial cylindromatosis.

Case Report & Histopathology

History of Present Illness

A 78-year-old white man was seen for numerous, asymptomatic lesions on his scalp. The patient states that the first lesion arose approximately thirteen years ago. He has continued to develop more lesions, which have slowly increased in size. The lesions are asymptomatic and have never bled or ulcerated. He has not sought medical attention for these lesions and has never tried any treatment for them (Figures 1, 2).

The patient’s past medical history is significant for colon cancer, which was diagnosed fifteen years ago, and treated with a hemicolectomy, chemotherapy and radiation at that time. The patient also has a past medical history of coronary artery disease, hyperlipidemia, and hypertension. The patient did not have a history of family or personal history of skin cancer.

The patient has ten siblings. One of his two sisters had similar lesion which were larger, more numerous, and first appeared in her mid 30’s. The patient did not think that his parents or any of his other 9 siblings had any had anything similar. He is the father of four daughters and grandfathers of two grandsons, ages 20 and 12 and two granddaughters, ages 26 and 15. None of these individuals has any had anything similar. He is suffering from familial cylindromatosis.9

Histopathology

Biopsy demonstrated islands of basaloid dermal cells with a ‘jigsaw puzzle’ pattern surrounded by a hyaline band. Within the islands, there were two cell types noted, the peripheral cells had small dark staining nuclei and were arranged in a palisading fashion and the more central cells had larger, pale staining nuclei. These findings are diagnostic of benign cylindromas (Figures 4, 5).

Review of Literature

Cylindromatosis has two presentations, the solitary, sporadic variant and the multiple, inherited variant. The multiple variant, which is referred to as familial cylindromatosis (OMIM #132700), is a rare autosomal dominant disorder with variable expression. There is a predisposition to multiple adnexal neoplasms. Familial cylindromatosis is also known as ‘turban tumor syndrome,’ because of the confluence of multiple cylindromas on the scalp, resulting in partial or complete hair loss.

Tumors begin to appear in the second to third decade, with a predilection for hairy areas. The tumors gradually increase in number and grow in size.1 In 1994, van Balkom and Hennekam reviewed the current publications and their personal cases and found the range of onset was from 1.5 years to 69 years, with the mean of 23.2 years. They also found that in a series of 74 cases of multiple cylindromas, 96% of those had scalp involvement, and 70% were in the nasolabial area, and back and chest at 43% and 42%, respectively.1 There is no sex or ethnic predisposition.

CYLD gene

Familial cylindromatosis (FC) is inherited with an estimated 100% penetrance by adulthood, but with variable expression.2 There can be a wide variety in the degree of expression even in the same family. The gene responsible is CYLD 1 gene, which was localized in 1995 to chromosome band 16q12-q13 and identified in 2000.4,5,6,7 The sporadic form was demonstrated to also be a result of a defect at 16q, as well 2, 4–6. Poblete Guitierrez et al. found that a single frame-shift mutation in the CYLD 1 was associated with the co-occurrence of cylindromas and trichoepitheliomas in a family suffering from familial cylindromatosis.3 Zhang et al. discovered by mutation analysis that frameshift mutation in the CYLD 1 gene was also responsible for multiple familial trichoepitheliomas (OMIM 601606), which has been previously linked to chromosome 9p21.5,11.12 Zhang et al. also proved that MFT and FC were allelic disorders caused by different mutations of the same gene and that CLYD 1 gene mutations are associated with several different phenotypes.10 The gene locus of 16q12-q13 has also been implicated in the Brooke-Spiegler syndrome, which is the occurrence of multiple trichoepitheliomas and cylindromas.12

The function of the gene was thought to be that of a tumor suppressor, however the exact mechanism of action had not been elucidated until recently. The CYLD protein operates in the TNF-a pathway by blocking the activation of NF-kB, which is an inhibitor of apoptosis. Therefore, a defect in the CYLD gene product allows for unrestricted cell proliferation, 13,14,15,16.
Origin of tumor cells

The cell-of-origin of cylindromas is still controversial. The coexistence of cylindromas and eccrine spiradenomas and previous studies add credence to the argument for an eccrine origin of cylindromas. However, the association of trichoepitheliomas and cylindromas favors an origin from a pluripotential cells with potentiality of primary epithelial germ cells, which would explain the formation of both hair structures and apocrine structures. This idea, supported by Leonard et al, who found loss of heterozygosity at chromosome 16q in numerous other adnexal tumors, besides cylindromas, suggesting origin from a pluripotential cell. In addition, there have been no reported cases of cylindromas involving the palms or soles, where apocrine glands are absent. At this time, there is currently no conclusive evidence for the cell of origin in cylindromas.

Malignancy

Patients affected with multiple cylindromas have no predisposition to basal cell carcinomas or squamous cell carcinoma, which originate from the epidermis. There is a small risk of cylindroma undergoing malignant transformation, which is quite rare. There are only 33 cases of malignant transformation in the literature. Individually, with multiple cylindromas appear to be at greater risk than those with solitary tumors. Gerretsen et al. reports that malignant tumors were distinguished from benign lesion by their rapid growth, long-standing ulceration, or bleeding. The histopathologic criteria of malignancy included tumor cell pleomorphism, frequent mitotic figures, with the loss of jigsaw pattern, peripheral palisading, hyaline sheaths, and dual cell population. In a review, by Gerretsen et al, 16 of 24 cases of malignant cylindromas, had extensive local infiltrative growth or distant metastases.

Treatment

Patients may want the tumors removed because they may occasionally be painful, but more frequently because they can be disfiguring. In a patient with numerous tumors, surgical excision can be limited to the tumors that are the most bothersome.
Conclusions

Cylindromatosis has two presentations, the sporadic form and the multiple variant form. The multiple variant is a rare autosomal dominant disorder with a proposed 100% penetrance, but variable expression. The variable expression was seen in our patient’s family history in which we addressed four generations and only a sister and the proband are affected. This patient had late onset of disease in his 60’s. His sister developed cylindromas in his mid 30’s. Cylindromatosis has not been reported to be associated with any systemic manifestations, unlike tuberous sclerosis, Muir-Torre, Gardner’s and Cowden’s syndromes, which also present with multiple adnexal tumors. Our patient's initial skin manifestations, unlike tuberous sclerosis, comprised of basal cell skin cancer, suggesting a possible relationship to the multiple variant form of cylindromatosis. Treatment of basal cell skin cancer is varied and may include Mohs micrographic surgery, carbon dioxide laser, and 5-fluorouracil. In this particular patient, treatment was performed with argon laser and resulted in improved cosmesis. However, due to a history of treated lesions, one of the patient’s tumors developed at age 41, indicating that some patients may be at higher risk for malignant transformation. Patients with familial cylindromatosis should be biopsied.

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32. Weyers et al used laser surgery as an inhibitor for the release of NF-kB. Therefore, aspirin may work in the place of the defective CYLD protein in preventing proliferation of new cylindromas. 13,14,15,16

Martins and Bartolo reported treating two patients’ scalp cylindromas using high energy (40-50W), continuous wave CO2 laser (Med-Hitac). They reported no recurrence of treated lesions, however one of the patients had areas of atrophy and alopecia following treatment. Weyers et al reported the use of electrosurgery, with only a few recurrences. The patient was satisfied with the cosmetic result. A new possible mechanism for the phosphorylaxis of cylindromatosis has recently been proposed utilizing the affect of aspirin on the TNF-a pathway. Aspirin functions in the TNF-a pathway as an inhibitor of the release of NF-kB. Therefore, aspirin may work in the place of the defective CYLD protein in preventing proliferation of new cylindromas.
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.
CLINICAL PHARMACOLOGY
Pharmacokinetics: In an open label, parallel group study in 24 patients with acne vulgaris, 12 patients (8 male and 4 female) applied 4 grams of Evoclin Foam once daily for five days, and 12 patients (8 male and 4 female) applied 4 grams of Clindagel® (clindamycin phosphate foam, 1%), once daily for five days. On Day 5, the mean Cmax, AUC(0-12) and AUC(0-24) were 22% and 25% lower, respectively, for Evoclin Foam than for Clindagel®

Following multiple applications of Evoclin Foam from lungs (20.2%) of the total dose was excreted unchanged after ≤ 12 hours on 12 days on 62.5 mg/kg)

CLINICAL STUDIES
Studies have indicated, randomized, double-blind, vehicle-controlled clinical trials with mild to moderate acne vulgaris used Evoclin (clindamycin phosphate) Foam, 1% or vehicle foam once daily for 28 weeks over a period of 3 months, and treatment was associated with a statistically significant change in acne severity of the vehicle for acne was not observed. The clinical course of this was that patients can be maintained at the same dose for up to six months, provided that the patient's acne has not worsened during this period.

The chemical name for clindamycin phosphate is methyl 7-chloro-6,7,8-trideoxy-6-(1-methyl-4-propyl-L-2-pyrrolidino)-1-thio-L-threo-2-thiopyranosyl-3-[(hydroxyphosphoryl)oxy]ethane-2-carboxylic acid.

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ADAMANTINOID TRICHOBLASTOMA/CUTANEOUS LYMPHADENOMA: A CASE REPORT AND REVIEW OF LITERATURE

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ABSTRACT

Cutaneous lymphadenoma is an uncommon benign tumor of the skin whose histogenesis has been debated in the literature. We report 3 additional cases of this tumor, all of which were located on the face. The histology of the lesions we report is consistent with past descriptions in which follicular and epithelial attachments as well as follicular germs are present. Immunohistochemical staining was performed on Case 1. The tumor cells were positive for high molecular weight keratin, CD 45, CD 30, S-100, and sparsely positive for CD 34. The tumor cells stained negative for EMA, PAS, and CD 20. The immunohistochemical staining pattern of these cases, the presence of epidermal and follicular attachments and the presence of follicular germs gives support to a follicular form of differentiation. Regardless of the histogenesis, cutaneous lymphadenoma is a benign entity that has been successfully treated by excision and has no published reports of recurrence.

Introduction

In 1987 Santa Cruz and Barr described 8 cases of what they called a lymphoepithelial tumor of the skin.1 In 1991 they renamed this benign tumor of the skin a cutaneous lymphadenoma.2 This tumor took on yet another designation in 1993 when it was classified as a nodular variant of trichoblastoma.3 To date, at least 46 cases of this entity have been reported in the literature. A review of literature shows the age at diagnosis to range from 14 to 75 (mean: 44) and that the ratio of males to females is 1.4:1. The typical clinical description is of an asymptomatic flesh colored papule or nodule. Most of the lesions were located on the head, with three located on the lower extremity. Common clinical impressions include a basal cell carcinoma and calcified cyst. All published reports of cutaneous lymphadenoma were cured by excision and no recurrences have been reported.

The histogenesis of this tumor has been debated in the literature. Santa Cruz and Barr initially speculated this tumor was differentiated from an immature pilosebaceous gland,4 which has been supported by several authors.1-12 Other suggested origins include basal cell carcinoma13 and sweat duct tumors.14-17 We agree with the authors whose histologic studies support follicular differentiation, a form of trichoblastoma. We report 3 additional cases of this tumor.

Case Report

We report a case (Case 1) of adamantinoid trichoblastoma on the forehead of a 50-year-old female. The clinical impression was that of a fibrous tumor. A review of our files, from 1995 until the present, yielded two additional cases of adamantinoid tri-

![Figure 1](image1.jpg)

Figure 1
Cutaneous lymphadenoma encased by fibrous tissue at periphery and composed of lobules of basaloid cells without distinct attachment to the epidermis. (20x)

![Figure 2](image2.jpg)

Figure 2
Well defined lobules of a cutaneous lymphadenoma encased with fibrous tissue and made up of several populations of cells and surrounded by a peripheral palisading layer of basaloid cells. (400x)

![Figure 3](image3.jpg)

Figure 3
Focal squamoid differentiation resembling squamous eddies with in the tumor lobules. (200x)

![Figure 4](image4.jpg)

Figure 4
Tumor lobule showing well defined indentation containing immature cells resembling a follicular germ. (200x)

Histology

The histopathologic features of our cases are similar to previously documented reports of adamantinoid trichoblastoma. Case 1 is a symmetrical, well-circumscribed lesion encased by fibrous tissue...
that does not, however, form a definitive capsule (Figure 1). Irregularly shaped lobules of cells were present in the dermis and showed minimal attachment to the epidermis. The lobules were composed of a peripheral layer of palisading basaloid cells that surrounded a mixed population of inner cells (Figure 2). The inner cell population included large, clear Reed-Sternberg like cells, small, mature lymphocytes and epithelioid cells. Some nests also exhibited areas of squamoid keratization resembling squamous eddies (Figure 3). A follicular germ was also present in this lesion (Figure 4). Fibroblastic stroma surrounded the nests and contained a variable number of lymphocytes. Cases 2 and 3 show a range of histopathologic findings, including some of those described in Case 1. Case 2 exhibited infundibular attachment (Figure 5). The amount of lymphocytic infiltrate in the lobules and stroma ranged from minimal in Cases 2 and 3 to significant in Case 1.

Immunohistochemistry

Immunohistochemical staining was performed on Case 1. The number of stains performed was limited due to the small size of the biopsy. The tissue was stained for high molecular weight keratin, CD 20, CD 45, CD 30, S-100, epithelial membrane antigen (EMA) and PAS. Case 3 was originally stained for L26, UCHL and CD 34. In addition, Case 3 was stained for CD 20 and CD 45.

CD 30 stained the large, clear Reed-Sternberg like cells within the lobules (Figure 6). Most of the lymphocytes in the tumor lobules and in the peripheral stroma stained positive for CD 45 in Cases 1 and 3 (Figure 7). CD 20 was essentially negative in Case 1 and rarely positive in Case 3. EMA was consistently negative in the tumor lobules. However, normal eccrine ducts at the periphery of tumor stained positive. Many dendritic cells were S-100 positive in the lobules of the tumor (Figure 8). High molecular weight keratin stained positive in the peripheral basaloid cells of the tumor lobules and scattered positive cells were also seen in the central portion of the lobule (Figure 9). CD 34 was sparsely and focally positive at the periphery of the tumor in the fibroblastic stroma and negative in the tumor lobules. The PAS stain was negative.

Discussion

Adamantinoid trichoblastoma is a rare benign tumor of the skin whose exact histogenesis remains uncertain. However, most authors seem to support a follicular differentiation, a form of trichoblastoma. A past study comparing the immunohistochemistry of cutaneous lymphadenoma, trichoblastoma, and basal cell carcinoma supports this classification. Follicular differentiation, in our cases, is supported by the high molecular weight keratin staining of the basaloid cells of the tumor, as well as, the epidermal and follicular attachments. In Case 2, there was a focus of epidermal and follicular attachment, as well as a follicular germ in Case 1. The presence of epidermal and follicular attachment have been described by other authors and suggest a follicular origin.

We were able to perform EMA and PAS, both of which were consistently negative and both of which showed positive internal control of the normal eccrine ducts at the periphery. Negative staining with EMA fails to support an eccrine differentiation as suggested by other authors who found positive EMA staining. It is not known whether positivity in these prior reports represents true eccrine differentiation or the entrapment of pre-existing structures. The failure of the stain in our material suggests that this tumor is not of an eccrine different ion. The fibroblastic stroma surrounding the nests contained a variable number of lymphocytes. This lymphocytic infiltrate stained negative with CD 20 and positive with CD 45. This is a finding consistent with other authors and indicates that the infiltrate is made up predominately of T lymphocytes.
and a lesser number of B lymphocytes. Variation in the number of lymphocytes might be explained as a function of the age of the lesion, with older lesions exhibiting a greater amount of infiltrate. However, future studies would be needed to support this.

Some authors have studied CD 34 and found it to be positive in the fibroblastic stroma surrounding the tumor lobule. This pattern of staining is found in trichoblastomas and trichoepitheliomas. In one of our cases, there was only sparse and focal positivity at the periphery of the tumor lobules. There has been one published report of a cutaneous lymphadenoma with desmoplastic stroma. However, this seems to be a rare finding.

The staining of the large cells with CD30 suggests these may be of lymphocytic differentiation, as seen in Hodgkin’s lymphoma. However, there is some variation among studies as to the number of CD 30 positive cells typically found in this lesion, as well as its histogenesis. Other authors have speculated that these cells may represent histiocytes or activated lymphocytes. Regardless of its histogenesis, adamantinoid trichoblastoma is a benign entity that has been successfully treated by excision. To date there have been no reports of a recurrence in any of the cases which have been published.

References:

Hyperhidrosis: A Review of Pathogenesis and Management


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**** Dermatology Program Director, Lutheran Medical Center, Brooklyn, NY

ABSTRACT

Hyperhidrosis is the excessive production of sweat in amounts greater than needed physiologically for thermoregulation. A literature review was performed concerning the pathophysiology, diagnosis and treatment of hyperhidrosis.

Introduction

Hyperhidrosis is a chronic disorder that can affect any part of the body, particularly the hands, axillae and plantar surfaces of the feet. (1) Although under reported, idiopathic hyperhidrosis has been estimated to affect 0.6-1% of the population according to a study of young Israelis. (2) A more recent survey of the United States population has shown a prevalence of 2.8% of individuals affected with hyperhidrosis, with only 38% of affected individuals discussing hyperhidrosis with their health care professional. (3) The disorder typically presents itself in childhood and adolescence and persists throughout life. Excessive sweating may be associated with social embarrassment and interferes in both personal and professional aspects of life. Sweating attacks may be precipitated by emotional stressors such as social situations or public speaking, high ambient temperature and ingestion of stimulants such as coffee. (4) Many treatment options have been offered to treat hyperhidrosis, including topical antiperspirants, oral medications, psychotherapy, iontophoresis, BOTOX injections, and surgery.

Background Information

Sweating is an integral function of the human body that maintains temperature, skin hydration and fluid and electrolyte balance. There are approximately 2 - 3 million sweat glands on the skin, including around 3,000 sweat glands per square inch on the palms of hands. Adults produce an average of 100 ml of sweat daily without excessive heat or exercise. With strenuous work or exercise, a person can produce 10 L per 24 hours. On average, there is an estimated 500 ml of water excreted in sweat per day. (5)

The most common form of hyperhidrosis occurs in the palms and soles (60%), but the condition also manifests in the axillae (30-40%) and face (10%). (6) Patients with hyperhidrosis exceed 12 to 30 times normal rates of eccrine secretion from palmar surfaces. Some patients may perspire 50 mg of sweat per minute in the axillae and others may produce 30 mg of sweat in the palms. (7) Secondary skin infections and bromhidrosis, odor due to perspiration, may occur due to the excessive moisture and maceration of the skin from the accumulation of sweat. (8)

Anatomy

There are three types of sweat glands -- eccrine, apocrine, and apocrine -- present on every part of the skin except the lips and glans penis. Eccrine glands, also known as merocrine glands, are located deep in the reticular dermis surrounded by a rich capillary plexus. Each gland consists of a single coiled secretory duct leading into an excretory duct which spirals upwards into the epidermis and opens onto the skin surface. (9) Eccrine glands secrete a dilute solution of urea, lactic acid and sodium chloride. (10) Eccrine glands regulate temperature by cooling the body through the evaporation of water from the skin. (11) They also function as a natural method to remove toxins from the body. Eccrine glands are found in the greatest density in the axillae, palms, soles and forehead. (12)

Apocrine glands play no role in thermoregulation and do not contribute to hyperhidrosis. These glands are different than eccrine glands in that they are larger and open into hair follicles. (13) They become most active at the onset of puberty and are seen in largest quantities in the axillae, perineum, and areolae. They are the phylogenetic remnant of the mammalian sweat gland and produce pheromones. Apocrine glands produce sex hormones, and thus, are responsible for an individual’s sexual scent. Sweat generated from apocrine glands is initially odorless and develops an odor only after interaction with skin bacteria. (14)

Apocrine glands are located in the axillae and appear during puberty. These glands are much larger than the eccrine glands and sustain copious amounts of fluid. (15)

Primary and Secondary Hyperhidrosis

There are two major types of hyperhidrosis -- primary and generalized. Primary, or idiopathic, hyperhidrosis is the most common form of this disorder. It typically is bilateral and symmetric, involving the axillae, palms, soles or face in individuals under the age of 25. (16)

Generalized hyperhidrosis may be the consequence of an underlying metabolic disorder, febrile illness or malignancy and...
usually presents in adults who suffer from sweating both during the day and at night. Other causes of excessive sweating include medications, metabolic disorders, menopause, spinal cord injuries, gustatory sweating, chronic alcoholism, subacute menopause, spinal cord injuries, gustatory sweating both during the day and at night. Usually presents in adults who suffer from excessive sweating.

Table I. Causes of Hyperhidrosis

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The workup for hyperhidrosis consists of several lab studies to exclude underlying disorders. This consists of thyroid function tests to exclude hyperthyroidism or thyrotoxicosis, urinary catecholamines to exclude pheochromocytoma, blood glucose levels to exclude diabetes mellitus or hypoglycemia, uric acid levels to exclude gout, and a purified protein derivative (PPD) to exclude tuberculosis. A chest x-ray may also rule out tuberculosis as well as neoplastic diseases. Lab tests are unnecessary if the presentation is characteristic of primary hyperhidrosis. (Table II)

Pathophysiology of sweating

Eccrine glands are primarily responsible for thermoregulation. Sweat production is normally controlled by the hypothalamus, which incorporates sensory information from the body to increase and decrease body temperature. Conductive heat loss is achieved through the diversion of blood flow to superficial vessels, while evaporative heat loss occurs with eccrine sweat secretion.

The sympathetic nervous system mediates eccrine and apocrine sweat gland function. Eccrine glands are innervated by cholinergic neurons which secrete acetylcholine at the sympathetic nerve endings, while apocrine glands are regulated by sympathetic adrenergic nerve fibers. Innervation of eccrine sweat glands begins in the hypothalamus, via the thalamus, and travels through the brainstem and medulla. The nerve fibers synapse at the intermediolateral cell nuclei of the spinal cord in the respective endocrine glands. Hyperhidrosis occurs as a result of a dysfunction of the central sympathetic nervous system and affects the hypothalamic nuclei, prefrontal areas and their cholinergic connections.

Sweating on the palms, soles and axillae is caused by emotional stress, while sweating on the face, chest and back is due generally to heat stimuli. Emotional sweating is regulated by the cerebral cortex, while thermal sweating is believed to be controlled by the hypothalamus. Therefore, emotional sweating does not occur while sleeping, while thermal sweating occurs throughout the day.

Sweating on the palms and soles can be either continuous or phasic. Continuous sweating occurs more frequently during the summer and is not precipitated definitively by emotional factors. However, phasic sweating occurs with minor emotional or mental activity and no difference has been noted between summer and winter months.

Histologically, there is no increase in the number or size of eccrine glands in patients with hyperhidrosis. It is believed that hyperhidrosis is caused by neurogenic over activity of normal number and normal sized sweat glands. Part of the neurogenic aspect of sweating may be heritable since 30% to 50% of patients have a family history of excessive sweating. Based on a prospective study published in the Journal of Vascular Surgery, there has been evidence that primary palmar hyperhidrosis is a hereditary disorder with variable penetrance and no sex-linked transmission.

Diagnostic Testing

The amount of sweating can be measured using several different techniques. The Minor starch - iodine test assesses the amount of sweat by placing a paper saturated with iodine, or placing a layer of iodine - starch mixture, on the affected area of skin. The skin is wiped with a brown - orange iodine solution and then lightly dusted with baking cornstarch powder. As sweat emerges from the eccrine glands, the iodide molecule and the starch in the powder produce a colorimetric reaction, causing the powder to turn deep purple. This technique enables the physician to map the exact location of active sweating and later use that original mapping as a reference for efficacy of treatment.

Gravimetric testing is used as a research tool to document response to treatment. Sweating is measured by placing filter paper in contact with the palm for a fixed amount of time and then weighing it.

Treatment

There are several treatments available to temporarily relieve symptoms of hyperhidrosis, including prescription - strength antiperspirants, aldehyde, oral anticholinergics, psychotherapy, iontophoresis, botulinum toxin type A (Botox) injections and surgical procedures.

Aluminum Chloride

Over the counter antiperspirants are beneficial for individuals with mild symptoms. These products usually contain aluminum and work by partially obstructing the opening of the sweat glands. Prescription strength antiperspirants, such as 20% aluminum chloride in alcohol (Drysol) or
Table III. Treatment Algorithms

<table>
<thead>
<tr>
<th>Axillary hyperhidrosis</th>
<th>Palmar hyperhidrosis</th>
<th>Plantar hyperhidrosis</th>
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<tbody>
<tr>
<td>1. Over the counter antiperspirants</td>
<td>1. Topical therapy with aluminum chloride</td>
<td>1. Topical therapy with aluminum chloride</td>
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<td>2. Topical therapy with aluminum chloride</td>
<td>2. Ionotophoresis</td>
<td>2. Tap water ionotophoresis</td>
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<tr>
<td>4. Surgery</td>
<td>4. Endoscopic thoracic sympathectomy</td>
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</tr>
<tr>
<td><strong>Plantar hyperhidrosis</strong></td>
<td><strong>Surgery</strong></td>
<td><strong>Psychotherapy</strong></td>
</tr>
</tbody>
</table>
| 1. Topical therapy with aluminum chloride | | Psychotherapy has limited effects in the majority of patients. Psychological problems are generally a result of hyperhidrosis, not the primary cause. Therefore, psychiatric care cannot cure this disorder, but may help the patient accept and cope with it. Benzodiazepines are helpful in reducing the emotional stimulus to excessive perspiration by decreasing anxiety. These agents should be used only for brief amounts of time in order to prevent problems with dependency. | Psychotherapy has limited effects in the majority of patients. Psychological problems are generally a result of hyperhidrosis, not the primary cause. Therefore, psychiatric care cannot cure this disorder, but may help the patient accept and cope with it. Benzodiazepines are helpful in reducing the emotional stimulus to excessive perspiration by decreasing anxiety. These agents should be used only for brief amounts of time in order to prevent problems with dependency. |}

6.25% aluminum tetrachloride (Xerac), are usually the first line agents. These topical treatments are applied 2-3 times a week, in the evening. It is believed that these agents mechanically obstruct the distal sweat gland ducts by facilitating the formation of a precipitate or by causing atrophy of the secretory cells. Burning and irritation are common side effects, especially when treating the axillae. Long-term use of antiperspirants sometimes results in the degeneration of the eccrine unit and resolution of localized hyperhidrosis.

**Aldehydes**

Topical aldehyde agents, such as formaldehyde and glutaraldehyde, are effective for the palms and soles, but are short-lasting. They reduce perspiration by occluding the sweat duct through denaturin g keratin at the top of eccrine pores. Obstruction of the sweat gland is localized to the superficial stratum corneum. Frequent application is necessary since epidermal regeneration within a few days reopens the lumen. Side effects include irritation and yellow-brown discoloration of the skin.

**Anticholinergics**

Oral anticholinergic agents competitively inhibit the binding of acetylcholine released preglandularly to its cholinergic receptor, thus blocking neuroglandular signaling. However, these agents lack specificity and therefore block normal physiologic cholinergic signaling, causing unappealing side effects. The adverse effects of anticholinergic medications consist of dry eyes and mouth, blurry vision and bowel and bladder function disturbances.

**Psychotherapy**

Psychotherapy has limited effects in the majority of patients. Psychological problems are generally a result of hyperhidrosis, not the primary cause. Therefore, psychiatric care cannot cure this disorder, but may help the patient accept and cope with it. Benzodiazepines are helpful in reducing the emotional stimulus to excessive perspiration by decreasing anxiety. These agents should be used only for brief amounts of time in order to prevent problems with dependency. Blocks have also been used to reduce emotional stimuli which leads to excessive sweating.

**Ionotophoresis**

Ionotophoresis is the least expensive treatment available for long-term results for localized areas of hyperhidrosis. The mechanism is not fully understood, but it has been thought to cause a temporary blockage of the sweat duct at the level of the stratum corneum. An ionized substance is introduced, by a direct current, through intact skin by placement of the patient’s hands in a bath of warm water or electrolyte solution with anticholinergic agents. A direct low-intensity current (15-18 mA), supplied by a D/C generator immersed in water, is directed across the palms or soles. The treatment stuns the sweat glands and decreases the secretion of sweat for approximately 6 hours to a week. Patients undergo three to four treatments per week, each lasting twenty to thirty minutes. Contraindications to treatment include pregnancy, cardiac pacemakers and metal orthopedic implants. Complications include temporary erythema of the treated skin with a transient rash and peeling and cracking of skin but such side effects have no long-term adverse effects. However, long-term maintenance treatments are required to keep patients symptom-free.

**Botulinum toxin therapy**

Neuromuscular blocking agents act at the neuromuscular junction of skeletal muscle and autonomic ganglia, inhibiting the transmission of nerve impulses. Botulinum toxin type A (Botox) has been approved by the Food and Drug Administration (FDA) in the treatment of hyperhidrosis based on results from two phase-three clinical studies. Botox has also proven successful in the treatment of cervical dystonia, facial wrinkles, spasticity and migraines. A clinical study involving 322 patients with excessive axillary sweating was performed. Fifty-seven out of 104 (55%) patients treated with BOTOX achieved an effective response, while only six out of 108 (6%) patients treated without Botox showed improvement. Eighty-four out of 108 (81%) Botox treated patients achieved greater than a 50% reduction in sweating, compared to only 44 out of 108 (41%) treated without Botox. Another study showed the median duration of response to BOTOX was 201 days or 6.7 months. There are several serotypes of the botulinum toxin. Two commercially available forms of the A serotype are Botox and Dysport. A new B serotype, called Myobloc in the United States and Neurobloc in Europe, was recently approved by the Food and Drug Administration for cervical dystonia. The A serotypes have been studied more and have had more clinical experience in the treatment of hyperhidrosis.

In large quantities, Botulinum toxin is responsible for a type of food poisoning known as botulism. When administered in small amounts, BOTOX inhibits the release of acetylcholine, preventing the transmission of nerve impulses to the sweat glands, resulting in decreased sweating.

Botox is used on the palms, soles and axillae with a total body surface area of the treated area being less than one percent. Topical or nerve block anesthesia may be used prior to injections, with the Minor starch-iodine technique used to identify the area being treated. The angle of the needle should be less than 45 degrees to prevent backflow, with the distance between injection sites ranging from 0.5 to 2 centimeters. Intracutaneous injections are commonly used rather than subdermal injections, since the latter are too close to nerve endings.

Repeated injections are required to maintain dryness and are effective from one to six months on average. Reported cases have shown the duration of anhidrosis in the axillae from 4-6 months, 3-12 months, to palmar treatment of an average of 6 months on the palms. It has been suggested that the palms do not have a longer duration of anhidrosis due to problems with backflow, smaller diffusion distance in thick palm skin, and the higher number of cholinergic nerve endings in palmar skin.

Aside from pain during injections, the most common side effect of Botox is bruising and mild soreness in the treated areas. Certain patients also exhibit weakness and instability of the lumbrical muscles of the hand. The weakness typically subsides and is spontaneously reversible. Botox is contraindicated if there is an infection at the proposed site of injection or a known hypersensitivity reaction to any of the ingredients in the formulation. In addition, patients with myasthenia gravis or Eaton-Lambert syndrome should use Botox with caution since they may be at an increased rate of developing spastic impairment or respiratory compromise.

Botox treatments have proven to be effective. There have been no reports of compensatory sweating in individuals treated in the palms or axillae.

**Surgery**

The major surgical methods for treatment of hyperhidrosis are sympathectomy, excision of affected glands and subcuta-
neous liposuction. Sympathectomy has been performed since 1920 and involves destruction of the ganglia responsible for hyperhidrosis. Thoracic ganglia 1 (T1) controls facial hyperhidrosis, thoracic ganglia 2 and 3 (T2 and T3) are responsible for palmar hyperhidrosis and thoracic ganglia 2, 3 and 4 (T2, T3 and T4) control axillary hyperhidrosis.29 Sympathectomy interrupts the nerve tracks and ganglia which transmit the signals to the sweat glands and treats palmar, facial and axillary hyperhidrosis.22 Endoscopic Thoracic Sympathectomy is considered a safe procedure and is minimally invasive.22 The rate of definitive cure is almost 100% if performed by an experienced surgeon.22

There have been several complications reported with endoscopic thoracic sympathectomy; compensatory sweating in previously unaffected areas (50-60%), gustatory sweating (5-10%), recurrence of hyperhidrosis, pneumothorax, intercostal neuralgia and Horner syndrome (1%). The cure rate is estimated to be 95-98% of patients with palmar hyperhidrosis, 75-80% with axillary hyperhidrosis and 25-50% of patients with plantar hyperhidrosis.31 Isolated plantar hyperhidrosis requires a Lumbar Sympathectomy, which is an open abdominal procedure, while diffuse hyperhidrosis of the trunk or generalized to the whole body cannot be treated surgically.

Other, less common surgical procedures and surgical excision of affected sweat glands, subcutaneous liposuction and subcutaneous curettage. Surgical excision is beneficial for axillary sweating since it removes the affected sweat glands. Subcutaneous liposuction is used to remove eccrine sweat glands that cause axillary hyperhidrosis. This procedure is associated with smaller scars and diminished hair loss in the affected area. Curettage is performed to destroy eccrine glandular tissue from beneath the skin surface.7

Alternative Treatments

Several alternative treatments have been used with some success in treating hyperhidrosis. These include biofeedback, hypnosis and several relaxation techniques.18,19 Several herbal remedies, such as St. John's Wort and chamomile, have been used; however, no well-documented clinical trials have supported these treatments.7

Management

Treatment for idiopathic hyperhidrosis is based on the severity and location of symptoms, and treatment options today have proven effective. Conservative measures should generally be attempted before more invasive treatments.22 Hornberger et al propose a protocol for the management and treatment of hyperhidrosis. They suggest criteria for establishing a diagnosis of primary hyperhidrosis -- excessive, visible sweating for at least six months without an apparent cause, with at least two of the following characteristics: bilateral and symmetric sweating, that impairs daily activities, frequency of at least one episode a week, age of onset less than 25 years, positive family history, and cessation of focal sweat during sleep. Secondary causes of excessive sweating must be ruled out to make a diagnosis of primary hyperhidrosis.31

Recent algorithms have been developed in treating the different types of hyperhidrosis. (Table III) First - line therapy for axillary hyperhidrosis is topical aluminum chloride antiperspirants. Botulinum toxin is second line treatment, followed by local surgery and sympathectomy.30 In selected cases, iontophoresis and systemic anticholinergic drugs may be attempted before surgery although there is a lack of convincing evidence for their effectiveness.31 In addition, iontophoresis is not used in the axillary region due to the location and difficulty of using an iontophoresis machine in the axillae.

First line treatment for palmar and plantar hyperhidrosis is topical aluminum chloride, followed by iontophoresis. If iontophoresis does not prove to be beneficial, botulinum toxin, systemic medications, surgery and sympathectomy should be attempted.30 Patients with plantar hyperhidrosis should be educated regarding local hygiene measures. These include changing socks twice daily, using absorbent foot powder twice daily and alternating pairs of shoes.30

Conclusion

Hyperhidrosis is a common disorder affecting up to 3% of the population. It can be a devastating condition to affected individuals, but there are several treatments available to manage it. The success of treatment depends on the severity of the problem and area of the body affected. However, newer treatment options offer patients a better prognosis.

References

Introduction

Among all occupational diseases, occupational skin disorders are known to be one of the most common. In fact, occupational skin diseases constitute approximately 10% of reported occupational diseases. However, this figure is likely an underestimate of the actual prevalence of occupational skin disorders due to a significant underreporting, by either the worker or physician, of skin disease in the occupational setting.

The definition of an occupational skin disorder is as follows: any abnormality of the skin that is a direct result of, or has been aggravated by, the work environment. In 1999, the highest incidence of occupational skin disease reported to the Occupational Safety and Health Administration was in the “agriculture, forestry, and fishing sector.”

Given the impact of skin disease on patients’ lives, as well as the financial loss to workers and their employers, the practicing clinician should be fully equipped to evaluate, diagnose, treat, and prevent occupational skin disorders. The intent of this review is to enhance the practicing clinician’s knowledge and recognition of occupational skin diseases, with special emphasis on performance of a comprehensive medical history with the occupational dermatology patient, so that the clinician can better serve his or her patients who have work-related skin diseases and disorders.

Initial Evaluation of Occupational Dermatoses

Initial evaluation of an occupational dermatosis consists of a routine medical history, as well as a complete occupational history including the following: (1) a detailed description of the patient’s current job activities, (2) a detailed description of all part-time and past jobs, (3) a history of the patient’s exposure to any hazardous agents, (4) a history of any home and hobby exposures, (5) a review of allergens and medications, and (6) a review of the use of any personal protective equipment and personal hygiene practices at work.

During the medical history, further evaluation should include asking the patient the following questions: (1) What do you think is causing the problem? (2) Do any co-workers have the same problem? (3) How is your condition on days off or on vacation? (4) Have there been any recent changes in your work practices? Effective diagnosis of many skin conditions requires a thorough investigation of occupational-related etiologies, whether the setting is primary care, occupational medicine, or dermatologic consult.

Investigation and Fact Finding

To obtain information related to the ingredients, physical properties, and adverse health effects of a chemical agent, it is advised that the health care provider ask the worker, employer, or manufacturer for copies of the Material Safety Data Sheets for the agents to which the worker is exposed. The federal Chemical Hazard Communication Standard (29 CFR 1910.1200) and “right to know” laws require employers to provide employees detailed information about hazardous chemicals used in the workplace. Finally, if necessary, one can visit the work-site, or arrange for a paraprofessional, to observe daily job activities.

Review of Common Occupational Dermatoses

The common occupational dermatoses consist of the following:

- Irritant Contact Dermatitis
- Allergic Contact Dermatitis
- Photosensitivity Disorders
- Acne and Folliculitis
- Disorders of Pigmentation
- Vascular Disorders
- Skin Cancer
- Connective Tissue Diseases
- Granulomas
- Disorders of Hair and Nails
- Infections and Infestations
- Conditions Caused by Physical and Mechanical Agents
- Systemic Diseases Due to Percutaneous Absorption

Irritant Contact Dermatitis

Irritant contact dermatitis accounts for 80% of all occupational skin diseases. Any substance in the workplace may act as an irritant and damage skin at the site of contact. Common irritants include: acids, alkalis, adhesives, glues, cement, aromatic chemicals, bacteria, fungi, chemical salts, foods, fiberglass, metals, oils and greases, plants, sawdust, soaps, detergents, solvents, ethylene oxide and other gases, tar and asphalt.

Symptoms of irritant contact dermatitis range from dryness to erythema, swelling, vesicles, and later exudation. Burning or stinging may also occur.

Irritant contact dermatitis reactions may be classified as acute, acute-delayed (8-24 hours following exposure), subclinical, chronic, or subjective (stinging and burning with a lack of clinical signs).

Many substances that produce an irritant contact dermatitis upon patch testing may not produce irritant contact dermatitis under actual conditions of exposure, which are less extreme. Thus, patch testing with irritants should be avoided. On the other hand, patch testing with allergens is useful for excluding allergic contact dermatitis as a diagnosis. Usually, patient history and unusual/asymmetric patterns upon exam distinguish irritant contact dermatitis from other disorders.

The primary treatment of irritant contact dermatitis involves eliminating exposure to the irritant or implementation of a substitute agent. In addition, it is important to protect the worker from exposure with gloves,
boots, facemask, apron, and/or coveralls.

The patient should be advised to avoid strong soaps and detergents that might cause further irritation but can be encouraged to use emollients and moisturizers. If clinically indicated, topical steroids may be used, and in severe cases, oral prednisone tapered over 2 weeks may be prescribed.

**Allergic Contact Dermatitis**

Allergic contact dermatitis is a Type-IV, delayed hypersensitivity, cell-mediated immune reaction. Once sensitization has occurred, even small amounts of repeat exposure to an allergen may cause dermatitis. Sensitization usually takes 7–10 days after first contact with the allergen. However, sensitization may take months or years to develop. Upon repeat exposure to an allergen, most reactions occur within 24–48 hours.


The symptoms of allergic contact dermatitis are clinically indistinguishable from irritant contact dermatitis. Definitive diagnosis of allergic contact dermatitis is via patch testing, whereas treatment is the same as that for irritant contact dermatitis.

**Photosensitivity Disorders**

In occupational dermatology, the two main photosensitivity disorders are: (1) phototoxic contact dermatitis and (2) photoallergic contact dermatitis. Phototoxic contact dermatitis occurs when an irritant on skin is activated by ultraviolet light. Photoallergic contact dermatitis occurs when a chemical on skin is converted to an allergen by ultraviolet light.

Photosensitivity disorders usually present as acute sunburns or eczematous reactions, in a photodistribution, at the site of exposure. Common photosensitizers include: furcocoumarins (natural chemicals) found in fruits and vegetables; polycyclic aromatic hydrocarbons in tar and creosote; perfumes; and medications. Clinical symptoms of photosensitivity disorders may involve erythema, edema, and possibly vesicles and bullae with later exudation. Burning or stinging may also occur and post-inflammatory hyperpigmentation typically follows.

The differential diagnosis includes porphyria, polymorphous light eruption, lupus erythematosus, and photosensitive drug eruption. Treatment is the same as for irritant and allergic contact dermatitis. Treatment should also include the recommendation for utilization of sunscreen and protective clothing. If the sensitizer is unknown, for further evaluation, the clinician may consider photopatch testing.

**Acne and Folliculitis**

There are a number of specific acne conditions that are related to the work environment. Acne mechanica may occur due to tight-fitting gear or clothing. Oil acne may occur secondary to oils and greases (petroleum or plant oils), halogenated aromatic hydrocarbons such as polychlorinated biphenyls, dibenzofurans, and dioxin). Typically, work-related acne presents as papules and pustules on the hands and forearms.

Chloracne may result from topical exposure to or ingestion of halogenated aromatic hydrocarbons. Chloracne typically presents as closed comedones and 1 mm to 1 cm cysts in the malar region of the face. Unlike the large, overactive sebaceous glands of acne, the glands of chloracne are disproportionately large.

Folliculitis may occur secondary to irritant chemicals or an infection and typically presents as small erythematous follicular pustules on the face, neck, forearms, hands, abdomen, buttocks, or thighs.

A history of exposure to oil, grease, asphalt, tar, et cetera is key to distinguishing acne and folliculitis from other conditions. Treatment consists of improvement of personal hygiene in the occupational setting, as well as topical or systemic antibiotic management. Oil acne usually resolves after exposure or contact with the offending agent is eliminated. It is noteworthy that chloracne is commonly resistant to pharmacologic treatment, including systemic tretinoin.

**Disorders of Pigmentation**

Contact with various agents in the workplace may produce increased and/or decreased pigmentation. Pigmentation may result from: inflammation, trauma, friction, exposure to dyes, coal tar, pitch, asphalt, creosote and furcocoumarins, chronic systemic intoxication from heavy metals (silver, mercury), and contact with foreign material that may be embedded via explosive forces.

Arsenic intoxication commonly presents with a diffuse hyperpigmentation pattern with dark macules or hypopigmentation (‘raindrops on a dusty road’).

Toxic vitiligo is due to chemical depigmentation at the site of contact with phenolic or catecholic derivatives encountered with exposure to rubber and plastic additives, photograph developing solutions, lubricating oils, adhesive resins, and cleaning solutions. With repeated contact, depigmentation may spread to distant body sites not in contact with the chemical. Also, toxic vitiligo may present with concomitant allergic contact dermatitis.

The differential diagnosis of toxic vitiligo includes: (1) natural tanning, which is usually lighter in color, and (2) idiopathic vitiligo, which occurs preferentially around body orifices, knees, elbows, dorsal hands, axillae, and groin.

Treatment of pigmentation disorders involves eliminating continued exposure to the offending agent in order to reduce the likelihood of permanent hypopigmentation or hyperpigmentation. Furthermore, hyperpigmentation usually resolves with time, however, localized hyperpigmentation may be treated with 2% hydroquinone. Hypopigmentation may be permanent; on the other hand, it may sometimes resolve and may later re-pigment with topical or oral psoralen ultraviolet A therapy.

**Vascular Disorders**

Urticaria is an allergic reaction consisting of wheals or hives and, perhaps, itching and redness appearing within 15–30 minutes following exposure, commonly via inhalation of an antigen. Contact urticaria is a reaction that may be classified as allergic or non-allergic. Flushing is a transient redness of the skin, primarily the face, which may occur with exposure to disulfiram (antabuse) used to accelerate curing in the rubber industry. Nonspecific causes of redness include: sun, heat, organic solvent vapors, and emotional stress. More often than not, urticarial lesions subside within 24 hours when exposure is eliminated. Also, 0.5% menthol in calamine may be used for its soothing properties; in addition, systemic antihistamines may be integrated into the treatment regimen.

**Skin Cancer**

Ionizing radiation may induce the following: radiodermatitis, pre-malignant actinic keratoses (AK), as well as squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and malignant melanoma (MM). Skin cancer is common in outdoor workers and may be seen in x-ray technicians and dentists. Actinic keratoses are small, flat, red macules with scales and may develop into SCC. Arsenic keratoses may become squamous cell carcinomas or basal cell carcinomas.

Keratoacanthomas (tar warts) are small, wart-like, papillomatous growths resulting from exposure to polycyclic aromatic hydrocarbons in soot, carbon black, coal tar, pitch, and certain oils. Keratotic papillomas may become SCCs, BCCs, or keratoacanthomas.

The differential diagnosis of occupational skin cancer includes: viral warts, seborrhoeic keratoses, and actinic keratoses.
Disorders of Hair and Nails

Toxic alopecia may occur 1-2 weeks following acute, toxic exposure to thallium-containing rodenticides, boric acid, arsenic, chloroprene, and high dose ionizing radiation. Traction alopecia results from trauma, e.g., catching hair in machinery. Hair and nail discoloration occurs secondary to chemical stains, e.g., yellow staining from nitrophenolic and other organic nitrates.

Nail shape and growth abnormalities are due to physical or chemical injury to the nail folds, e.g., absorption of pesticides into the nail fold. Treatment involves removal from exposure.

Infections and Infestations

Infectious agents that cause occupational skin disease may include: bacteria, fungi, viruses, rickettsia, protozoa, metazoa, helminths, and arthropods.

Common bacterial infections and associated occupations include: (1) staphylococcus/streptococcus – agricultural workers, butchers, meat packers, slaughterhouse workers, (2) cutaneous and atypical mycobacteria – farmers, vets, butchers, pathologists, fishermen and aquarium keepers, (3) tularemia – hunters, vets, farmers, butchers, fur handlers, (4) brucellosis – farmers, vets, slaughterhouse workers, meat packers, livestock workers, (5) anthrax – sheep and wool handlers, butchers, farmers, and (6) erysipeloid – meat and fish handlers.

Common viral infections and associated occupations include: (1) herpes simplex – health care workers, (2) viral warts – meat and wool handlers, sportspersons, and (3) orf – shepherds.


Common parasitic infections and associated occupations include: (1) cutaneous leishmaniasis – tropical forest workers, (2) helminths – skin divers, lifeguards, dock workers, (3) scabies – nursing home and hospital workers, and (4) lyme disease – outdoor workers, loggers, ranchers.

Treatment of occupational skin infections and infestations is the same as that for the general population.

Conditions Caused by Physical and Mechanical Agents

Physical and mechanical agents that may result in occupational skin conditions include: heat, cold, ultraviolet light, electricity, wind, radiation, vibration, friction, pressure, etc. Milia is a common condition manifested by swelling and obstruction of the sweat gland ducts following exposure to heat and humidity. Milia presents as small, pruritic, red papules. Electrical burns may produce tissue damage presenting with erythema to blisters and necrosis. Often the damage is much deeper than clinically apparent. Blisters or calliosties occur due to friction. Treatment involves eliminating exposure. Milia may improve with drying lotions (calamine). Chapping and dermatitis from low humidity may be treated with moisturizers and low-potency topical steroids.

Systemic Diseases Due to Percutaneous Absorption

Toxic systemic diseases may result from exposure via skin absorption. Skin absorption may be increased by the following: (1) entrapment of substance against skin due to rubber gloves, clothing, etc., (2) damage to the stratum corneum, (3) damage to the skin from cuts, lacerations, abrasions, etc., and (4) contact of a toxic substance with specific anatomic areas of the skin (e.g., genital, eyelid, and facial areas).

Chemicals that may cause systemic toxicity are as follows: (1) aniline dyes – methemoglobinemia, liver disease, and bladder cancer, (2) arsenic – peripheral neuritis, gastrointestinal and cardiac disturbances, (3) benzene – acute myelogenous leukemia, aplastic anemia, and myelofibrosis, (4) cyanide salts – cellular asphyxia and death, (5) mercurials – nephritis, gastroenteritis, central and peripheral nervous system abnormalities, (6) methyl-n-butyl ketone – peripheral neuropathy, (7) polyhalogenated aromatic hydrocarbons – liver disease and porphyria, (8) organic solvents – central nervous system abnormalities, (9) neuromuscular insecticides – cardiovascular, gastrointestinal, and neuromuscular abnormalities, and (10) hydrofluoric acid – hypocalcemia, hyperkalemia, and hypomagnesemia.

Treatment of systemic diseases due to percutaneous absorption focuses on reversing the systemic toxicity.

Conclusions

The practicing clinician has an obligation to perform a thorough medical history and physical exam with specific attention paid to the patient’s occupational and environmental history. The practitioner
who has knowledge of the agents utilized and the conditions that are associated with the occupational environment will be at an extreme advantage in diagnosing occupationally-related skin disease. Finally, the clinician should create a comprehensive treatment plan for each patient, but, at the same time, he or she should not forget to address issues of prevention in the workplace.

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Pemphigus Foliaceus in Association with Lisinopril

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ABSTRACT

Pemphigus foliaceus is a cutaneous autoimmune blistering disease. Environmental factors, including numerous drugs, are thought to play a role in its pathogenesis. Drugs that induce pemphigus are generally divided into two groups according to their chemical structure: thiol (sulfhydryl [SH]-containing) and non-thiol drugs. Lisinopril is a non-thiol drug that contains an active amide group, which can trigger acantholysis and may potentially cause a more severe and protracted course of pemphigus. This is a case report of a patient who developed pemphigus foliaceus after taking lisinopril.

Case Report

A 52 year-old Hispanic male presented with three week history of a "burning" and pruritic rash on his head and chest. Clinical examination revealed multiple verrucous and crusted, erythematous papules and plaques that were scattered over the face, chest, abdomen, back, buttocks and extremities (Figure 1). There were several eroded and hemorrhagic areas with rare flaccid vesicles and bullae. Nikolsky sign was positive. The patient's mucous membranes were clear.

The patient's medical history included diabetes mellitus, hypertension, hypercholesterolemia and seasonal allergies. His medications upon presentation included lisinopril and atorvastatin. The lisinopril was started approximately 5 months prior to the onset of his rash.

A total of three punch biopsies were performed, two for hematoxylin and eosin staining (H&E) and one for immunofluorescence. The first H&E biopsy showed a subcorneal pustule with acantholysis in the upper epithelial cell layers. In the dermis, there was a mixed inflammatory infiltrate composed of lymphocytes, neutrophils and eosinophils (Figure 2). Based on the fact that the split appears to be within the upper layers of the epithelium, the diagnosis of pemphigus foliaceus or pemphigus erythematosus was favored. The second H&E biopsy showed a subcorneal blister containing acantholytic cells and a mixed cell infiltrate with eosinophils present around venules of the superficial plexus. These findings were also consistent with pemphigus foliaceus/erythematosus. Immunofluorescent stained sections demonstrated intercellular staining of the epithelium with IgG and C3. The IgM, IgA, and fibrinogen stains were negative.

The antinuclear antibody was negative, ruling out the diagnosis of pemphigus erythematosus. Intercellular substance antibody was positive (1:20 titer). The basement membrane zone antibody, endomyssial IgA antibody, and gliadin antibody IgG and IgA were all negative.

A diagnosis of pemphigus foliaceus (PF) was made and drug induced PF was suspected. The patient's lisinopril was discontinued after consulting with his primary care physician. He was started on a treatment course of systemic prednisone. In addition to corticosteroids, several steroid-sparing agents were prescribed, including azathioprine, dapsone, and mycophenolate mofetil. Due to the changing status of our patient's medical coverage, it was difficult to maintain a consistent treatment regimen. Although the patient did experience episodes of improvement in his disease, his condition remains active two years after his initial presentation.

Discussion

Pemphigus foliaceus is generally a benign variety of pemphigus. It appears most commonly in the elderly, but can affect people of any race, age or sex. Other than the cutaneous manifestations of PF, patients are usually in good health.

Typically the disease presents with small, fluid-filled blisters most commonly on the face and scalp. As the disease progresses involvement of the torso and extremities is seen. Because the vesicles and bullae form in the upper layers of the epidermis, they rupture very easily, as a result, erosions and crusts may be the only clinical findings. On the face, scalp and upper trunk the lesions are often scaly or crusty on a red and inflamed base. Patients sometimes experience a burning sensation or localized pain. Unlike pemphigus vulgaris, pemphigus foliaceus is characterized by a chronic course, with little or no involvement of the mucous membranes. The superficial blisters in PF are induced by IgG autoantibodies directed against the cell adhesion molecule, desmoglein 1 (160 kD), expressed mainly in the granular layer of the epidermis.

It is well established that pemphigus foliaceus may be drug induced. Some of the more commonly reported causative agents include penicillamine and captopril.

Drugs that induce pemphigus are generally divided into two groups according to their chemical structure: thiol (sulfhydryl [SH]-containing) and non-thiol drugs.

Most of the drugs reported to provoke the onset or relapse of pemphigus are thiol drugs. These drugs possess powerful acantholytic qualities in vitro. The role that the sulfhydryl radical group plays in producing pemphigus in vivo has been extensively studied. It has also been demonstrated that "masked" thiol drugs, which are drugs that may undergo metabolic changes to form thiol (sulfur-containing) groups, can induce pemphigus. Thiol-induced pemphigus usually presents as the foliaceus variant and has a more...
favorable prognosis than the pemphigus vulgaris variant upon drug withdrawal.\textsuperscript{5} Non-thiol drugs are thought to have an active amide group in their molecular make-up that allows acantholysis to occur. These drugs may share a chemical structure that is capable of triggering pemphigus.\textsuperscript{7}

Captopril, an angiotensin converting enzyme (ACE) inhibitor, is a frequent cause of pemphigus. Of the ACE inhibitors, captopril is the only one that contains a thiol group in its structural make-up. Another ACE inhibitor, lisinopril (C21H35N3O7), does not contain a thiol group, but it does contain an amide group. Lisinopril is a derivative of the active metabolite of enalapril.\textsuperscript{9} Enalapril has been reported to induce pemphigus in vivo \textsuperscript{10,11} and induce severe acantholysis of keratinocytes with suprabasal clefting in vitro. In fact, it has been shown in vitro that enalapril can produce acantholysis in a shorter amount of time and at one-tenth the concentration of thiol drugs.\textsuperscript{4} Drugs with an active amide group are thought to result in a more severe and chronic manifestation of disease.\textsuperscript{7} Therefore, lisinopril may potentially cause a more severe and protracted course of pemphigus.

It has been shown that when the causative agent of pemphigus is a non-thiol drug, there is only a 15% chance that spontaneous recovery will occur upon withdrawal.\textsuperscript{5} There has been only one other reported case of pemphigus foliaceus in association with lisinopril in the literature. Unlike our patient, this patient’s rash improved greatly within 48 hours of discontinuation of lisinopril, although follow-up in this patient was limited to three weeks secondary to death from unrelated causes.\textsuperscript{9} Two years after our patient’s initial presentation, his condition remained active, despite discontinuation of lisinopril.

References:
Drug Induced Eccrine Gland Necrosis in a Patient with Altered Mental Status: A Case Presentation and Review

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ABSTRACT

Background: Drug induced bullae with eccrine gland necrosis is a rare clinicopathologic entity most often reported with a comatose state. It is associated with bullae formation on pressure surfaces within twenty-four hours of drug overdose and self-resolution within fourteen days.

Subject: We report a case with histopathologic features of bullae and sweat gland necrosis in a non-comatose patient with altered mental status. The report is unique as the patient developed bullae on therapeutic drug doses over the global body surface with course complicated by necrotizing fasciitis.

Conclusion: Drug bullae and eccrine necrosis cases have been reported predominantly in drug overdose coma patients with lesions developing over pressure surfaces. This case provides evidence for development of this rare reaction in a patient with therapeutic drug levels and over the global body surface. A comprehensive review of the clinical, pathophysiologic, pharmacologic and histopathologic findings associated with this condition are summarized.

Introduction

Drug induced cutaneous bullae with eccrine gland necrosis is a rare but well described phenomenon. The first published case report was reported in 1812 by Napoleon’s surgeon, Larry. He reported cutaneous blisters in soldiers with carbon monoxide induce coma. But it was not until 1963 that the characteristic histopathologic findings of eccrine necrosis were discovered in association with barbiturate induced coma. Similar entities have been reported sporadically over the years, occurring most frequently in barbiturate overdose coma patients with lesions developing over pressure surfaces. This following case involves a non-comatose patient with altered mental status that develops drug induced bullae with eccrine necrosis over the global body surface with only therapeutic doses of phenobarbital and lorazepam.

Case Study

A 50 year-old female was admitted for altered mental status after being found on the floor of her apartment due to an apparent hydroxyzine overdose. Upon examination, the patient was confused with slurred speech. She stated that she had tripped on her way to the bathroom and complained of hip pain. The patient had been diagnosed with a seizure disorder one month prior to this incident. Additionally, her admission toxicology screening was positive for benzodiazepines but levels of prescribed antiepileptic were undetectable. She was placed on phenytoin and phenobarbital for seizure prophylaxis and ciprofloxacin for treatment of UTI. Lorazepam was added the following day for agitation and anxiety. On day three of admission the patient developed a tense bullous eruption on bilateral thighs, buttocks and inguinal area (Figure 1), which extended to the abdomen, back, neck and arms over the following day (Figure 2). A punch biopsy was performed at two sites, which demonstrated histopathological evidence of subepidermal bullae formation (Figure 3) and eccrine gland necrosis (Figure 4). Dermatopathology revealed no evidence of inflammatory infiltrates. Phenobarbital and lorazepam were discontinued with resolution of bullae within 7 days. Unfortunately, several ruptured sites developed secondary MRSA infection complicated by necrotizing fasciitis which required extensive surgical debridement and skin grafting.

Review of Literature

Drug induced bullae with eccrine gland necrosis has been most frequently associated with barbiturate overdose; however, several other drugs have been implicated (Table 2 adapted from ref. 10). The majority of drug-induced bullae cases are reported in association with barbiturate overdose; however, several other drugs have been implicated (Table 2 adapted from ref. 10). The drug-induced bullae may be attributed to a greater tendency for barbiturates than other drugs to decrease cutaneous oxygen consumption. Bullous eruption with therapeutic drug levels as illustrated in our case is very rare. Note however that our patient was given two drugs well associated with bullae development and it is plausible that a synergistic effect was observed. With the advent of new medications over the past few decades, the case reports of drug induced eccrine gland necrosis has increased. Most recently chemotherapeutic agents idarubicin and cytokine arbinoside have been implicated. Although...
toxicity has been related to specific drug classes, similar histological findings have been cited in non-drug-induced coma.\textsuperscript{7, 8} This implies that pharmacologic induction alone is insufficient for bullous formation. Additionally, it is important to note that an event of coma blisters does not preclude the further use of inducing drugs in patients, as evidenced by several cases of drug re-introduction after resolution of bullae.\textsuperscript{6, 7}

The characteristic bullous lesions of this condition are typically few in number, which generally localized over peripheral IV sites\textsuperscript{6}, pressure surfaces or bony prominences. These lesions generally appear within 24 hours of drug overdose and self-resolve in 7-14 days after drug cessation. Sweat gland necrosis differentiates drug induced coma lesions from bullae due to other etiologies.\textsuperscript{16, 17} In one study, biopsies from 7 patients were analyzed and the results indicate that the secretory portion of the eccrine gland is the first and most susceptible to necrosis followed by other adnexal structures and lastly the epidermis.\textsuperscript{9} Vascular changes correlated proportionately with epidermal damage and consisted of neutrophilic inflammatory infiltrate of arterioles. These findings contradict a former theory that pressure is the main cause of cutaneous changes in drug induced coma.\textsuperscript{18} All immunoglobulin studies performed show no evidence of a drug hypersensitivity reaction. The pathophysiologic of drug-induced eccrine gland necrosis is not completely understood. It is known that ischemia from local pressure effects fragile eccrine gland first\textsuperscript{19} but this does not account for cases of global body eruption. The suppression of respiratory and circulatory function in coma patients may lead to generalized hypoxia and subsequent epidermal necrosis,\textsuperscript{3} but this implication has not been supported by histological studies. Excretion of drug metabolites via eccrine glands with direct toxicity induced necrosis has also been implicated\textsuperscript{20} but is not supported by histological studies. Other immune mediated mechanisms have also been proposed with various immunoglobulins identified by direct immunofluorescence of epithelial cells and adnexal structures.\textsuperscript{8} However, this is a nonspecific finding, possibly a normal physiologic reaction to tissue injury. Although none of the current theories account for all of the various case reports, an interplay of these mechanisms may link differing patient histories to this unique clinical entity.

The differential diagnosis in cases of drug and coma induced bullae is neutrophilic eccrine hidradenitis. This is a self-limiting, inflammatory condition most commonly caused by chemotherapeutic agents in immunocompromised patients. It is histologically differentiated from drug-induced bullae by the presence of drug associated neutrophilic infiltrate.\textsuperscript{17}

The treatment of drug induced bullae with eccrine necrosis is supportive. Since 27% of total body heat loss occurs via sweat evaporation\textsuperscript{31} and eccrine function is compromised in this condition, monitoring for hyperthermia is essential. Interestingly, there is no evidence of progression of bullous lesions to toxic epidermal necrolysis. However, the natural course of bullae expansion and rupture leaves the subcutaneous tissues susceptible to secondary infection. This can progress to sepsis and/or necrotizing fasciitis as seen in our patient. Such complications are rare but devastating.

Due to the uncommon nature of bullae with eccrine necrosis and the variations in case history and presentation, it is difficult to confer direct causation to CNS depression or pharmacologic action. Rather it is evident that these are predisposing or initiating factors in a condition without clear pathophysiologic mechanisms. Since the course is self-limiting, underlying autonomy or infection is unlikely. Certainly prospective studies will be most informative to determine the pathogenic mechanisms of this entity but such studies would be extremely difficult given the rarity of occurrence. More realistic may be a retrospective study quantifying degree of hypoxia, cutaneous circulatory losses, drug dosages and degree of CNS depression in relation to bullae development. From this we may build a risk profile by which to identify patients at greatest risk for eccrine necrosis and develop prospective studies of greatest insight.

Acknowledgments
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<th>CNS Disorders</th>
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Table 2: Drugs Associated With Eccrine Gland Necrosis

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IN CONJUNCTION WITH
THE AMERICAN OSTEOPATHIC ASSOCIATION

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OCTOBER 23-26, 2005
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We are all proud that our college has its own journal, the JAOCDD. I am soliciting my fellow AOCD members to sit on the editorial review board of the JAOCDD. I give my utmost thank you to the current members of the JAOCDD editorial review board for all of their help in reviewing manuscripts to be considered for publication. If you would be interested in helping improve the JAOCDD by reviewing 1-2 resident manuscripts every three to four months, please contact me. Your help would be greatly appreciated and you will be listed as a member of the editorial review board in each issue of the journal. Please consider becoming an integral part of the Journal of the American Osteopathic College of Dermatology.

Sincerely,

Jay S. Gottlieb, D.O.

Editor JAOCDD
Jay1953@aol.com
Phone-954-963-5875
Pemphigus Foliaceus

A 31-year-old Hispanic American male reported to our clinic with a one-month history of a rash which first presented on the face and then quickly spread to the upper chest, back, scalp and thighs. The lesions began as erythematous papules that over several days developed into red, weeping erosions that would not heal. The patient described the lesions as stinging and burning without pruritus. He did not feel systemically ill.

Examination revealed a well appearing male with numerous erythematous, weeping erosions, distributed on the malar cheeks, the central chest and back. There was lesser involvement of the scalp and thighs (Figures 1 and 2). Many lesions exhibited a ring of scale and some lesions were crusted (Figures 3 and 4). Nikolsky’s sign could be elicited at the periphery of the erosions. No oral or ocular lesions were seen.

Except for the cutaneous lesions, the patient’s medical history and review of systems were unremarkable. He had never had a similar cutaneous eruption in the past. He reported being in good health with no chronic medical conditions and had no history of hospitalizations or surgery. There was no family history of similar diseases. He related a negative personal or family history of cancer. He denied taking any medications, either prescribed or over the counter. The patient is employed as a truck driver of non-hazardous cargo. Travel history included several trips yearly to Mexico to see family. He denied any travel to central or South America.

The differential diagnosis after examination included: pemphigus foliaceus, bullous impetigo, pemphigus erythematosus, subacute cutaneous lupus erythematosus and pemphigus vulgaris.

Two 4-mm punch biopsies were obtained from the left upper arm for H&E and immunofluorescence studies. H & E pathology specimens revealed superficial acantholysis with supppuration between the stratum corneum and the superficial granular layer as well as a mixed inflammatory cell infiltrate in the dermis consistent with either a superficial blistering disorder or bullous impetigo. (Figure 5) Direct immunofluorescence (DIF) studies of peri-lesional skin revealed IgG and complement deposition in the epidermis. Indirect immunofluorescence (IIF) was positive with a 1:80 titer for intracellular substance antibodies (Ab) and negative for the basement membrane zone antibodies. Studies for ANA, HIV and RPR were negative. Aerobic bacterial cultures were positive for moderate growth of Staphylococcus Aureus. A CBC and a CMP were within normal limits.

Based on the clinical presentation, dermatopathology and microbial culture results, the patient was diagnosed with pemphigus foliaceus with a secondary bacterial infection. Treatment was initiated with oral prednisone at a dose of 60 mg qd. Topical triamcinolone acetonide 0.1% cream (TAC) and clobetasol propionate foam 0.05% were started for the skin and scalp lesions, respectively. In addition, cephalaxin 500 mg tid for 7 days was utilized to address the staphylococcal infection. The lesions improved over the next several weeks, at which point methotrexate (MTX) was started as a steroid-sparing agent.

Clinical Course

The patient was gradually tapered off of oral steroids and the MTX was increased based on clinical presentation. After approximately 2 months of therapy he had completely discontinued prednisone and was taking 12.5 mg of MTX per week. Over the next 6 weeks the dose of MTX was increased to 15 mg qw to attain adequate control. The frequency of new lesions had reduced to approximately 2-4 per week. TAC and clobetasol foam continued to be applied topically to any new lesions.

Discussion

Epidemiology

Pemphigus foliaceus is a rare superficial blistering disorder whose frequency varies by the population studied. In Western
affected. The average age of onset for non PEMPHIGUS FOLIACEUS: A CASE REPORT WITH REVIEW OF LITERATURE

The lesions may exhibit both positive Nikol-

rheic areas of the face, chest and back. A superficial blisters which quickly denud into

shallow weeping erosions and are distrib-

uted with a greater density in the sebor-

rhic areas of the face, chest and back. The lesions may exhibit both positive Nikol-

sky's sign and Asboe - Hansen sign. Over time, the lesions may coalesce to

form large denuded areas. Patients often complain of stinging or burning but will have surprisingly few other complaints. In fact, those afflicted are otherwise in good health. An important physical feature that distinguishes pemphigus foliaceus from pemphigus vulgaris is the absence oral lesions.

Histopathology
Well-formed lesions of pemphigus foli-

aceus are characterized by superficial bul-

lae with the cleft occurring in the granular cell layer or just beneath the stratum corneum. Fibrin and occasional neutrophils may be present. A superficial dermal infiltrate composed of neutrophils and eosinophils is usually present. Immunofluorescence studies revealed IgG and complement deposition within the intracellular space of the epidermis with a predilection for the superficial epidermis in both clinically normal and affected skin. However, the staining pattern with direct immunofluorescence (DIF) is often nonspecific with a more generalized pattern of immunoglobulin deposition being seen. Immunofluorescence studies revealed IgG and complement deposition within the intracellular space of the epidermis with a predilection for the superficial epidermis in both clinically normal and affected skin. However, the staining pattern with direct immunofluorescence (DIF) is often nonspecific with a more generalized pattern of immunoglobulin deposition being seen.6,7

Pathogenesis
The blistering of pemphigus foliaceus is
induced by deposition of IgG antibodies directed at desmoglein-1. This molecule, along with desmoglein-3, is critical to proper cell-cell adhesion through desmosoma-

mal structures. In the epidermis desmoglein-1 is expressed more promi-

nently in the superficial regions near the granular layer and its dissolution explains the superficial blister formation of pemphi-

gus foliaceus. This is in contrast to pemphi-

gus vulgaris where the IgG antibodies may be directed at only desmoglein-3 or to both desmoglein-1 and desmoglein-3. Antibod-

dies directed at only desmoglein-3 disrupt primarily oral mucosa, as this is the pre-

dominant adhesion molecule present in this mucosal tissue. This results in the well-

known oral erosions that herald pemphigus vulgaris. Antibodies directed against both desmoglein types 1 and 3 results in full thickness epidermal dissolution as well as the mucosal lesions seen in pemphigus vulgaris.8,9

Pemphigus Subtypes
Subtypes of pemphigus are generally
recognized. Due to the patient's hispanic ethnicity, Fogo Selvagem, a subtype endemic to Central and South America is important to consider. This variant is thought to have an infectious etiology, perhaps viral, spread by the black fly, Simulium pruinatum. The presumed infection then induces an auto immunity to desmoglein type 1 which in turn induces blistering. This is supported by the high prevalence of Pemphigus Subtypes
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recognized. Due to the patient's hispanic ethnicity, Fogo Selvagem, a subtype endemic to Central and South America is important to consider. This variant is thought to have an infectious etiology, perhaps viral, spread by the black fly, Simulium pruinatum. The presumed infection then induces an auto immunity to desmoglein type 1 which in turn induces blistering. This is supported by the high prevalence of

Another important variant to consider is drug induced pemphigus. Frequently reported inciting agents are penicillamine, captopril and nifedipine, although many other drugs having been implicated. The clinical and histopathological appearance is identical to classic pemphigus foliaceus. It is theorized that the pharmaceuticals form a hapten with desmoglein resulting in anti-

genicity and production of anti-desmoglein antibodies. Most patients go into remission when the drugs are discontinued. Our patient not any medications at the time of onset of his blistering disorder.10

Pemphigus erythematosus is believed to be a localized type of pemphigus with lupus erythematosus like features including malar distribution of lesions, positive ANA and basement membrane antibody deposition. (7) Our patient's seborrheic distribu-

tion, negative ANA and lack of basement membrane antibodies distribution excluded this subtype. Paraneoplasic pemphigus is associated with a striking stomatitis as well as an association with non-Hodgkins lymphoma (42%), chronic lymphocytic leukemia (25%) and other malignancies. There was no evi-

dence of malignancy in the patient's evalu-

ation.11, 12, 13, 14

IgA pemphigus presents with pustules, which coalesce into annular patterns with central crust. As opposed to IgG antibod-

dies, IgA is the predominate antibody directed against surface components of keratinocytes.15 Lastly, pemphigus herpeti-

forms presents with urticarial plaques and eosinophilic spongiosis.14,15

Lab studies
A punch biopsy for H&E combined with

DIF is a generally adequate to diagnose pemphigus foliaceus. The H&E stain pro-

vides information on the level of the blister formation and cell types present while DIF elucidates the type and location of the immune globulin deposition. When there is widespread deposition of immunoglobulins within the full thickness of the epidermis, it may not be possible to ascertain definitively if pemphigus vulgaris or pemphigus foliaceus is the underlying disease. In such cases indirect immuno-

fluorescence (IIF) is often helpful. IIF utilizing different substrates such as monkey or guinea pig esophagus will show a different pattern of immune globulin deposition for pemphigus foliaceus versus pemphigus vulgaris. Generally, IIF is not a reliable single test for pemphigus foliaceus due to the
rare occurrence of pemphigus like antibo-
dies in some normal patients.16

Enzyme linked immunosorbent assay
(ELISA) is also available to test the sera of suspected pemphigus foliaceus cases. ELISA can detect not only the presence of anti-desmoglein antibody but can specific-
ify identify their target as either anti-
desmoglein-1 or anti-desmoglein-3 antibo-
dies. Armed with this knowledge pemphigus foliaceus may be distinguished from pemphigus vulgaris. In addition, quan-
titative testing of circulating antibodies can measure disease activity.17,18,19

**Differential Diagnosis**

Several other entities may have a clinical presentation similar to pemphigus foli-
aceus. Pemphigus vulgaris may present with weeping ulcers distributed in sebor-
rehic areas. However, oral lesions, which often herald the onset of pemphigus vul-
garis, are not seen in pemphigus foliaceus.2 In addition, H & E staining of biopsy specimens of pemphigus vulgaris will reveal a deep blister with 'tomb stoning' of basal keratinocytes adherent to the basement membrane secondary to unaf-
fected hemidesmosomal attachments. As discussed earlier, DIF and IIF studies will also reveal blister formation occurring lower in the epidermis in pemphigus vul-
garis.6,7

Bullous impetigo may present with ery-
therematous blistering and weeping ero-
sions. Histopathologically, pemphigus foliaceus and bullous impetigo both show a superfi-
cial blister in the epidermis. This is explained by the finding that exfoliative toxin-A, produced by Staphylococcus Aureus, cleaves desmoglein-1 resulting in blister formation similar to pemphigus foli-
aceus.20,21 However, in bullous impetigo no immunoglobulin deposition will be seen during DIF or IFF studies. It should be noted that cultures from pemphigus foli-
aceus lesions are often positive for Staphy-
lococcus or Streptococcal bacteria, but this is not typically a significant finding.6,7

Subcutaneous lupus erythematous (SCLE) may present as red scaling lesions but seldom has prominent blister formation. SCLE lesions are typically photo distributed as opposed to the seborrheic distribution of pemphigus foliaceus. H&E will reveal hydropic degeneration of basal ker-
atinocytes and dermis will have an infiltrate of lymphohistiocytic cells. On DIF, a granu-
lar deposition of multiple types of immunoglobulins is typically seen at the basement membrane as well as surround-
ing hair follicles. Occasionally a granular deposition of immunoglobulin may be noted in the epidemis of SCLE.4,7,22

Other disease processes to consider would include linear IgA dermatosis and subcorneal pustular dermatosis (SCPD). In linear IgA dermatosis, a linear deposition of IgA antibodies is seen along the basement membrane as opposed to the IgG found in the epidermis in pemphigus foliaceus. Sub-
corneal pustular dermatosis begins as po-
cyclic lesions with superficial pustules. Although histologically similar to the IgA subtype of pemphigus foliaceus, the lack of antibody deposition in SCPD helps to dis-
tinguish these two entities.5

**Treatment of pemphigus foliaceus**

Prednisone is the mainstay of pharma-
cological therapy for pemphigus foliaceus. Doses of 1.0 mg/kg/day are started and the number of new lesions forming is used to measure the effectiveness of the treat-
ment. A response is expected within 1-2 week. Topical corticosteroids may be applied to new lesions as they appear as an adjunct to limit inflammation and blistering. In some cases topical steroids alone may be effective.7

Corticosteroid sparing agents must fre-
quentely be utilized for adequate long-term control of severe pemphigus foliaceus. Our patient experienced good results with methotrexate. As with all cases of methotrexate use, CBC, CMP, liver function testing and periodic liver biopsy are required. Concomitant folic acid supple-
mentation is recommended.22

In more difficult cases of pemphigus foli-
aceus, other immunosuppressive medica-
tions may be utilized. Azathiprine and mycophenolate are popular agents used alone or in conjunction with steroids. A pri-
mary advantage to these agents is the poten-
tial for clinical remissions of pemphi-
gus foliaceus for limited periods.12,13 Hepa-
toxicity is a limiting side effect. Cyclophosphamide was found to be effec-
tive as mono therapy for pemphigus foli-
aceus with complete remission obtained in 17 of 20 study patients. Interestingly, when relapses did occur the disease was less severe than during previous occurrences demonstrating a disease modifying ability. Severe side effects such as sterility, hemor-
rhagic cystitis, leukopenia and increased incidence of neoplasia vaping the drug is indicated.3

In a recent study of 11 patients, intra-
venous immunoglobulin (IVIG) was suc-
cessful at inducing complete remission in resistant cases of pemphigus foliaceus. All patients were undergoing therapy with other immunomodulatory agents without adequate results. After addition of IVIG, a complete and sustained remission was obtained for up to 18 months after IVIG was discontinued. No adverse side effects were noted.24 A second smaller study of six patients yielded similar results.25

Plamapheresis is a useful therapy in order to quickly lower antibody titers for patients with severe, recalcitrant disease. It is frequently utilized with other immunosup-
pressive modalities to prevent a rebound in antibody titer after the therapy is discontin-
ued.26 Complications include electrolyte imbalances, pulmonary edema, hypoten-
sion and need to maintain venous access.14

Other agents reported to be have been used with limited success include: tetryc-
cline, nicotinamide, dapzone, plaquenil and gold.12,18

**Conclusion:**

Pemphigus foliaceus is a relatively rare disease with diverse etiologies. While not frequently life threatening, it is disfiguring, may be painful and may require significant immunomodulatory therapy for adequate control. Our case demonstrates many of the features of classic pemphigus foliaceus and exemplifies a realistic level of control that can be achieved through the use of steroids and methotrexate. We believe methotrexate is a good choice for the gen-
eral dermatologist due to familiarity of use with other dermatologic conditions, ease of administration and known side effects pro-
file.

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Trichostasis spinulosa (TS) is a condition in which telogen hairs are retained predominantly in sebaceous follicles. Although it is a relatively common skin disorder, it is often overlooked. We report a case of TS in an elderly gentleman and discuss various treatment options.

Case Report

The patient was a sixty-nine year-old Caucasian man who was seen for actinic keratosis. Upon further examination, there were several black, pinpoint follicular lesions on his nose with soft hairs projecting from the surface. These lesions were similar in appearance to open comedones (Fig 1-2). The contents of several of the follicles were expelled with an acne extractor, fixed to a slide using Acrymount™ mounting medium, and examined microscopically. The diagnosis of trichostasis spinulosa was made at this time.

Discussion

Trichostasis spinulosa is a common disorder of hair follicles that gives the appearance of open comedones. When examined closely, however, bundles of soft hair that project 2 to 3 mm above the skin surface can be seen. When examined microscopically, the hairs are round at the proximal end and shredded distally (Fig 3-5). The most common locations are on the nose, forehead, shoulders, and back especially in the intrascapular region. Although it has been reported in ages ranging from 17 to over 60 years, it is classically and predominantly found in the elderly and middle-aged. A second, pruritic variant has been described mostly in young adults. These lesions are most typically seen on the trunk and upper arms. The affected follicles may contain up to 50 vellus hairs and mild perifolliculitis may be present. Pityrosporum and bacteria, specifically Propionibacterium acne, may be a possible etiologic factor of this disease. However, the precise cause of TS is still unknown.

Although there is no cure for TS, several treatment regimens have been tried with varying success. Keratolytic preparations have been implemented either as a sole therapy or after the application of a wax depilatory. However, depilation can be time consuming if large areas require treatment. In the past, application of 0.05% tretinoin solution applied daily for two to three months had been suggested as the most effective form of treatment. Today, 0.04% and 0.10% tretinoin gel microsphere (Retin-A Micro®) can be used in its place. Hydroactive Adhesive Pads (Biore®) have been used with success as well. A recent study examined the use of an 800-nm pulsed diode laser in treating TS in thirteen subjects with skin phototypes III, IV, and V. This study found complete clearance of the dark plugs for 8 to 12 weeks after two treatments with the additional benefit of smoother skin.

References

Case Report:

A 55-year-old Caucasian male presented to the clinic complaining of a pruritic rash on his scalp, upper extremities, chest, and back for approximately thirty years. He believed the rash began while he was serving in Vietnam. In the preceding year, he had developed hyperkeratotic nails of the right hand and scaling of his right palm. His rash had been unsuccessfully treated in the past as psoriasis with topical/intrale- sional corticosteroids, acitretin, and cyclosporine. Several years prior to his presentation, he had undergone one treatment of broadband UVB phototherapy that resulted in a cutaneous burn. He admitted to being extremely sensitive to the sun. He also believed his condition became worse in the summer.

His past medical history was significant for a positive RPR test with a titer of 1:4 for several years, however his confirmatory test, microhemagglutination test (MHATP) was repeatedly negative. He denied headaches, joint pain, kidney problems, sexually transmitted diseases, fever, night sweats, fatigue, or weight loss. He had a history of depression /anxiety and neck pain for which he took sertraline (Zoloft) and ibuprofen. The patient had no medication allergies. He did not abuse alcohol, tobacco, or any other illicit drugs. He denied having any family members with skin problems, connective tissue disease, or autoimmune disorders.

On examination there were verrucoid hyperkeratotic plaques symmetrically involving the chest, back, upper extremities. He had both hyperpigmented and hypopigmented patches along the vertex of the scalp with atrophy centrally. There was a diffuse erythema of the malar and forehead regions. The oral and genital mucosa was found to be normal. There were five hyperkeratotic, yellow dystrophic nails with scaling on the right hand palm.

A 4mm punch biopsy was performed on the patient’s right arm and it was sent for H & E, which revealed a hypertrophic lichenoid dermatitis with features of both lupus erythematosus and hypertrophic lichen planus. A second 4mm punch biopsy for direct immunofluorescence, was also performed from the right arm of non-lesional sun-protected skin. The direct immunofluorescence showed granular IgM along the basement membrane consistent with lupus erythematosus. The patient had a total of six previous biopsies that were obtained and reviewed. Two years prior he had underwent two biopsies one from a verrucous plaque from the left arm and the second from an eczematous patch on the right abdomen. The left arm was consistent with hypertrophic lichenoid dermatitis with features of both hypertrophic lichen planus and verrucous lupus erythematosus and the second from the right abdomen showed interface dermatitis more consistent with lupus erythematosus. Interestingly, his first biopsy from four years prior showed clearly lichen planus from a violaceous plaque on his back.

Complete blood count, basic metabolic panel, thyroid panel, HIV, hepatitis panel and liver function tests were within normal limits. As previously stated, he had a positive RPR (1:4 titer) but a negative MHATP. A negative ANA (repeated twice) and a positive SSA. Also he had a negative SSB, Smith, and RNP antibodies. His urinalysis was completely normal. A KOH preparation of the scale from the right palm was positive for hyphae consistent with tinea manum.

Hydroxychloroquine 200mg twice a day was instituted after obtaining a negative glucose-6-phosphate dehydrogenase. He was referred for ophthalmology consult prior to starting the medication. He was instructed to use sun-protection including physical blocker sunscreen and sun-avoidance. Initially he felt the medication helped, however after six months there was little improvement except for decrease in pruritus. He made the choice to discontinue conventional treatment for an additional six weeks of sun-avoidance. A KOH examination of the scale from the right arm mycologically improved after a six week course of terbinafine.

Discussion

Lichen planus –lupus erythematosus (LP-LE) overlap syndrome is a condition that has clinical, histopathologic, and/or immunofluorescent patterns of both diseases at the same time. Lichen planus and lupus erythematosus are not uncommon diseases, however they rarely occur together.1 There has been approximately 50 cases of LP-LE overlap syndrome reported in the literature.2

Previous case reports of LP-LE overlap syndrome comprise a very heterogeneous group with some having features favoring LE or LP. The clinical features of LP-LE overlap syndrome have included various features including violaceous papules and plaques on the dorsal acral skin, follicular plugging, verrucoid plaques with atrophy, and mucous involvement.1 While others have reported hair loss, nail involvement and photosensitivity to be prominent clinical features.2 Several reports have shown a predilection for acral skin and oral mucous. There are several different systemic abnormalities that have been associated with LP-LE overlap syndrome. For example, Jamison et al reported a patient with LP-LE overlap syndrome with low C4 and mixed cryoglobulinemia.4 In summary, many different clinical and systemic features are noted in patients making the diagnosis difficult.

In a few case reports, the passage of time allowed for one to diagnosis LE or lichen planus. During the course of disease, systemic lupus erythematosus has also declared itself in a few case reports with the presentation of additional serologic and noncutaneous manifestations.3

It is important to differentiate between lupus erythematosus and lichen planus because it has an effect on treatment and prognosis of patients. Therefore, physicians must try to distinguish them by using...
all diagnostic tests available. LP and LE display some similar histologic features however there are a few findings that favor one diagnosis over the other. For example, colloid bodies are more numerous in lichen planus along with basement membrane cleft formation (Max-Joseph spaces). In lupus erythematosus, basement membrane thickening is a common feature. Immunofluorescence can sometimes be helpful. A linear band of fibrinogen at the basement membrane zone is consistent with lichen planus. Whereas, granular deposits of immunoglobulins at the basement membrane zone is consistent with lupus erythematosus. However, as in our patient this distinction is not always possible thus the diagnosis of LP-LE overlap syndrome was made.

This disease overlap syndrome tends to have a chronic course and be very treatment resistant. Various treatment options have been tried including systemic retinoids, cyclosporine, dapsone, hydroxychloroquine, and thalidomide.

References:
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Lichen Planopilaris: A Case Presentation and Review of the Literature

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ABSTRACT

A sixty-nine year old female presented to the office with a one year history of scalp pruritis, scaling erythematous plaque-like lesions and cicatrical hair loss. Dermatological evaluation and biopsy resulted in the diagnosis of lichen planopilaris (LPP). LPP is a rare, progressive inflammatory condition of unknown etiology that causes irreversible scalp hair loss. Early diagnosis and treatment is paramount in order to prevent scarring from occurring. This case study reviews the clinical presentation, histopathology, differential diagnosis, and treatment options of LPP.

Case Report:

A sixty-nine year old female presented to the office with a one year history of scalp pruritis, scaling erythematous plaque-like lesions and cicatrical hair loss. Dermatological evaluation and biopsy resulted in the diagnosis of lichen planopilaris (LPP). LPP is a rare, progressive inflammatory condition of unknown etiology that causes irreversible scalp hair loss. Early diagnosis and treatment is paramount in order to prevent scarring from occurring. This case study reviews the clinical presentation, histopathology, differential diagnosis, and treatment options of LPP.

Discussion

Scarring alopecias are due to permanent damage to essential parts of the hair follicle or destruction of the entire hair follicle. They are classified into the categories of primary scarring alopecias, where the hair follicle is the principal target of destruction, and secondary scarring alopecias, where the follicular damage is a secondary consequence to impingement of the follicular unit.

The differential diagnosis of primary scarring alopecias includes lichen planopilaris (LPP), pseudopelade, and discoid lupus erythematosus. Lichen planopilaris is a rare inflammatory condition that causes permanent scalp hair loss. The pathogenesis of LPP is poorly understood. Patients initially present with erythema, perifollicular scaling and hyperkeratotic follicular papules. The hair follicles are subsequently destroyed, yielding atrophic, irregular, angular or polygonal shaped patches of alopecia with similar follicular papules at the periphery of the patch of alopecia. Symptoms vary from moderate to severe scalp itching, pain, burning and discomfort. Lesions of LPP may be insidious or fulminant, involving focal or widespread areas of the scalp. Lichen planus in other areas of the body including mucous membrane and nails may occasionally precede, occur simultaneously or follow scalp involvement. LPP is reported more frequently in women with the onset varying from late childhood to the seventh decade. Longitudinal ridging of the nails was evident (see photo 4). Anti-nuclear antibody (ANA) was negative. A punch biopsy was taken at two sites revealing telogen hair follicles with cystic dilation surrounded by a lichenoid infiltrate of lymphocytes and histiocytes at the level of the dermal-epidermal junction. The inflammatory infiltrate demonstrated vacuolar degeneration involving the follicular epithelium and increased fibrosis in the reticular dermis. The diagnosis of lichen planopilaris was made and the patient was subsequently treated with topical corticosteroids (clobetasol). Her symptoms have been well controlled with occasional exacerbation.

Figure 1

(melanophages). In more developed lesions, perifollicular fibrosis and epithelial atrophy at the level of the infundibulum and isthmus are characteristic findings. Damage to the hair bulge, the site where stem cells of the hair follicle are currently accepted to reside, results in permanent scarring alopecia. Immunofluorescence in active stages shows cytid body staining by anti-IgM and/or anti-IgA, IgG and rarely C3 at the level of the dermal-epidermal junction.

The clinical triad of scarring alopecia, loss of pubic and axillary hairs and the progressive development of hairy follicular papules variously located is known as the Graham-Little syndrome.

The clinical presentation of pseudopelade of Brocq (PB) is similar to LPP. There is controversy over the etiology of PB. PB may represent either a distinct entity (i.e., an idiopathic primary scarring alopecia) or the terminal stage of...
of treatment is to alleviate symptoms and to impede progression. Intralesional and/or Group I and II topical steroids are used as the initial treatment for localized LPP. In instances of rapid progression, oral corticosteroids may be considered to limit the acute inflammation. Topical glucocorticoids relieve itching; nevertheless, the lesions resolve slowly. Antimalariais (hydroxychloroquine) and retinoids (isotretinoin) may be effective in the long-term treatment of LPP, requiring months to years for improvement and resolution.\(^3\) Cyclosporine, a calcineurin inhibitor that acts by suppressing gene transcription of IL-2, has been successful in treating severe and refractory lichen planus of the skin, and has produced sustained remission in numerous patients with LPP.\(^4,5,10,11\)

While the mechanism of action of cyclosporine in lichen planus is unknown, cyclosporin is presumed to involve the selective inhibition of T-helper cells and down-regulation of cytokines responsible for T-cell adhesion to keratinocytes.\(^6\)\(^,\)\(^7\)

There have been a few cases of thalidomide induced remission of lichen planopilaris.\(^17\) Thalidomide most likely exerts its beneficial effects in patients with LPP by affecting tissue cytokine concentrations such as TNF-\(\alpha\) down-regulation.\(^8\) However, benefit-to-risk analysis is essential due to the potentially adverse effects associated with thalidomide - most notably teratogenicity. A recent study suggests that thalidomide is ineffective in treatment of LPP.\(^17\)

One study analyzed the phenotype of the inflammatory infiltrate present in scarring alopecia.\(^5\) The histology, direct immunofluorescence (DIF) and immunohistochemistry of lichen planopilaris revealed a prominent infiltrate of CD3+ cells with a high CD4+/CD8+ ratio, variable numbers of macrophages, mast cells and fibroblasts always fewer than lymphocytes. Interferon (INF)-gamma was also present.\(^9\) This data suggests that T-helper cells may be involved in the pathogenesis of LPP. Therefore, a trial of immunomodulator agents such as topical tacrolimus or pimecrolimus may be a reasonable therapeutic modality in recalcitrant LPP.

**Conclusion**

Lichen planopilaris is a rare inflammatory condition of uncertain etiology that causes irreversible scalp hair loss. Like other scarring alopecias, LPP involves either destruction of the hair follicle or scarring of the reticular dermis. Due to the progressive nature of LPP, prompt diagnosis and treatment is essential in order to prevent scarring. Cutaneous biopsy is essential for the diagnosis of LPP. The primary objective of therapy is to alleviate symptoms, and to impede or slow progression of the disease.

**References:**

Herpes Simplex and HIV Infection: A Case Report and Review of the Literature

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ABSTRACT

Herpes progenitalis is a common infection most frequently caused by herpes simplex virus 2 (HSV-2). In the early 1980’s chronic perianal herpetic ulcers came to the forefront, largely due to the impending human immunodeficiency virus (HIV) epidemic. Genital herpes and other genito-ulcerative diseases (GUDs) are clearly risk factors for concomitant HIV infection. In immunocompetent patients, a reactivation of an HSV infection typically heals within one to two weeks. In contrast, severely immunosuppressed patients, such as those with advanced HIV infection, present with a more chronic course. We describe a case of recalcitrant genital herpes manifesting as the initial presentation of HIV disease. A review of the literature was also performed on PubMed using the keywords: HIV and herpes simplex.

Case Report:

A 37 year-old African-American male was admitted to the hospital for evaluation and treatment of purulent ulcerations in the genital region of three months duration. He had been treated by his primary care physician several times on an outpatient basis with topical clotrimazole and betamethasone dipropionate as well as oral antibiotics. A previous inconclusive biopsy report revealed “a non-specific acute and chronic inflammatory infiltrate with benign sweat gland proliferation”.

The patient denied any history of illicit drug use, unprotected sexual encounters, homosexual behavior, sexually transmitted diseases, blood transfusions, or tattoos. He denied any specific past medical conditions or surgical procedures. The review of systems was unremarkable except for the painful ulcers in the groin.

Physical examination showed multiple, well demarcated, punched out ulcers that coalesced in the periscrotal and perianal areas (figures 1 and 2). Painless, inguinal, nonsuppurative lymphadenopathy was present bilaterally. The rest of the cutaneous exam was unremarkable. Laboratory examination revealed a white blood cell count of 3.4 X 103; otherwise, the remainder of the hemogram and metabolic profile was within normal limits. A bacterial culture of the ulcerations grew normal flora, the RPR was non-reactive, and a viral culture was not yet obtained.

Empirically, the patient was treated with systemic azithromycin and acyclovir and topical tepid burrows solution compresses. Biopsies that were obtained from the border and center of the ulcers was consistent with consistent a herpes virus infection (figure 3). HIV serologies were positive, and the CD4 count was 234. The patient improved and was discharged on acyclovir. He was scheduled for follow-up with the infectious disease service to commence highly active anti-retroviral therapy (HAART) and prophylaxis against other opportunistic infections.

Comment

The herpes virus contains double stranded DNA that replicates in the cell nucleus and is characterized by the ability to produce latent but lifelong infection. Epidemiologic surveys suggest that HSV-2 is the most common cause of genital ulcerations among the sexually transmitted diseases. It is estimated that currently in the United States, 23% of adults are infected with HSV-2, of which of up to 20% are completely asymptomatic.

In the setting of HIV infection, the clinical presentation of anorectal diseases may be atypical. In fact, unusual features of herpes simplex or varicella infections should prompt one to consider an underlying HIV infection.

Although there is debate in the literature, the majority of studies suggest that HSV-2 and other genito-ulcerative disease (GUDs) are actually risk factors for HIV acquisition. It is possible that a preexisting HSV infection could increase the pathogenicity of HIV since the two viruses may act as cofactors. This concept is termed reciprocal enhancement. Keratinocytes, unlike macrophages and T helper cells, lack the CD4 molecule that is the required receptor for entry of HIV-1 infection. Heng et al was the first to report an in-vivo co-infection of HIV and HSV-1 in keratinocytes and macrophages. They demonstrated that the virions in the co-
infected cells were larger, morphologically atypical, and appeared to be hybrids of one another. Since AIDS patients have been reported to shed more HSV, to acquire more chronic HSV infections, and to have produced multiple acyclovir resistant strains this questions the need for incorporating chronic suppressive treatment for HSV-2 in the treatment of AIDS. 11, 12, 13, 14

Treatment modalities for HSV and HIV have focused on anti-viral therapies and safe sex practices. Unfortunately, no effective vaccines are available for HSV or HIV. Complicating matters is the emergence of acyclovir resistant strains of HSV. In most instances, acyclovir, valacyclovir, and famciclovir are effective antiviral therapies for HSV. 15 Foscarnet has successfully been used as an alternative in acyclovir resistant cases; however, foscarnet resistant strains have also been isolated. Spermicides such as nonoxynol-9 and gramycin have also shown anti-HSV and anti-HIV activity but are not recommended as sole prevention strategies. Specifically, identifying and counseling the asymptomatic carrier of HSV is necessary if we are to decrease the transmission of genital herpes and potential HIV co-infection.

Conclusion

Since the emergence of HIV in the early 1980’s, the prevalence, presentation, and pathogenicity of GUDs, including HSV, have changed dramatically. An emphasis should be placed on treating any underlying STD since any GUD may carry an increased rate of transmission of HIV. Our focus should be on early identification and treatment of the asymptomatic shedding of HSV in AIDS patients and to continue to work towards new antiviral therapies and vaccines.

References:
X-Linked Ichthyosis

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ABSTRACT

A case report of an adult male with X-linked ichthyosis is presented along with the pathogenesis, histopathology, differential diagnoses, laboratory evaluations and treatments for the disease. X-linked ichthyosis is a clinically mild eruption due to a genetic disorder of keratinization and is recessively inherited with incidence second to ichthyosis vulgaris. It is found in males at birth and is due to a steroid sulfatase deficiency. Scaling is found in a distinct distribution and extracutaneous manifestations are possible. Typically, hyperkeratosis and a normal to thickened granular layer are seen on dermatohistopathology.

There are numerous ways to make the diagnosis in affected patients and carriers and these are reviewed. Treatment is aimed at eliminating and preventing scale.

Introduction

X-linked ichthyosis is an interesting dermatological disease process which has been studied extensively. In 1966, Wells and Kerr classified the various ichthyoses. In 1976 steroid sulfatase (STS) deficiency was identified by Jobsis et al and in 1978, Shapiro et al showed the relationship between X-linked ichthyosis and a STS deficiency.1,2

The skin manifestations typically develop at birth or early infancy with light scaling which progresses to larger, dark scales affecting the extensor and sometimes flexor regions of the extremities in addition to preauricular areas, neck and upper trunk. The palms and soles are generally uninvolved. Asymptomatic corneal opacities and cryptorchidism as well as delayed labor in mothers of affected patients are associated features.4

Case Report

A thirty-two year old Caucasian male presented to the office for treatment of “dry skin all my life”. He described a lifelong history of diffuse, dry and scaling skin on his trunk and extremities noted to be worse in the winter months. His birth history was unremarkable for any prolonged or difficult labor and he had no history of descended testes. However, the patient and his wife did have difficulty conceiving for approximately one year prior to presentation.

The patient’s past medical and surgical history included a unilateral herniorrhaphy. His family history included a nephew with hospital. He smoked one pack of cigarettes per day and had approximately four drinks per week. The patient worked as a material food handler.

On physical examination diffuse adherent, plate-like brown scales were noted on the trunk, posterior and lateral neck and extremities with accentuation over the extensor surfaces and relative sparing of the flexures. His face, palms and soles were spared. See Figure 1.

Laboratory data from our patient included a peripheral blood fluorescence in situ hybridization (FISH) study positive for a STS deficiency. This study was performed using molecular cytogenetics. A DNA FISH probe using cultured T lymphocytes from the peripheral blood of our patient and a STS probe specific for the short arm, p portion, of the X22 chromosome was applied. Using the STS probe which hybridizes within band Xp22.3, a lack of hybridization to the X chromosome was shown. This was consistent with a microdeletion specific for X-linked ichthyosis. See Figure 2.

Peripheral blood FISH study for Kallman syndrome was negative showing a normal pattern of hybridization at band Xp22.3. Serum lipoprotein electrophoresis including serum cholesterol, triglycerides, chylomicrons, beta lipoproteins, pre-beta lipoproteins, and alpha lipoproteins was also performed and showed a normal pattern. Urology and ophthalmology consults were obtained and were both within normal limits.

A punch biopsy from the right leg showed thickened and compact hyperkeratosis and hypergranulosis. See Figure 3.

Discussion

X-linked ichthyosis is a clinically mild skin eruption due to a genetic disorder of keratinization. It is the second most common form of ichthyosis after ichthyosis vulgaris. X-linked ichthyosis affects between one in 2,000 and 6,000 males and has no racial or geographic predilections. It typically develops at birth or early infancy usually between two and six weeks of age and

Figures 1a & 1b
Diffuse adherent, plate-like brown scales on trunk and extremities with accentuation over extensor surfaces
extracutaneous manifestations are possible.3

Mild, light colored scaling is seen in the neonatal period. Over the ensuing weeks, the scales become yellow-brown, polygonal and firmly adherent eventually progressing to large, dark scales often giving the skin a dirty appearance. The abdomen is usually more involved than the back and the scales are more prominent over the extremity surfaces, pre-aurocular areas, neck and upper trunk with or without flexural involvement. Generally, sparing of the palms and soles is seen and hair and nails are normal. The condition generally improves in the summer and worsens in the winter.1

In 1966, Wells and Kerr classified the
50

X-LINKED ICHTHYOSIS

undescended testes. Abnormalities of testis and testicular cancer with progression may be seen due to placental factor, prolonged labor and failure to deliver the male patient. Sperm count and abnormal sexual maturation are detectable by slit lamp examination. Female carriers and 50-100% of affected males present in adulthood in 24% or more of cases. They may not affect visual acuity. They may be seen at the arrow, this was positive for a STS gene deletion.

Figure 2
Fluorescence in situ hybridization (FISH) study positive for STS deficiency. The internal control and enzyme presence should both occur at the centromere location with the green dot as control and red dot as enzyme gene presence. Since only the green dot is seen at the arrow, this was positive for a STS gene deletion.

Figure 3
H & E of right leg showing thickened hyperkeratosis and hypergranulosis (20x)

various ichthyoses. In 1976 steroid sulfatase deficiency was identified by Jobsis et al and in 1978, Shapiro et al showed the relationship between X-linked ichthyosis and a STS deficiency.

Extracutaneous manifestations are possible in X-linked ichthyosis patients. Affected males and female carriers may have comma shaped corneal opacities on the posterior capsule or Descemet’s membrane. These opacities are asymptomatic and do not affect visual acuity. They may present in adulthood in 24% or more of female carriers and 50-100% of affected male patients and are detectable by slit lamp examination. The presence of corneal opacities is helpful in making the diagnosis. During the birth of the affected patient, prolonged labor and failure to progress may be seen due to placental STS deficiency. In addition, affected male patients have an increased risk of cryptorchidism and testicular cancer with reports of such cancer presenting without undescended testes. Abnormalities of sperm count and abnormal sexual maturation as well as hypoplasia of the penis and scrotum have also been reported. Other phenotypical abnormalities are rarely seen including short stature, mental retardation, chondrodysplasia punctata (a form of dwarfism), and Killian syndrome (hypogonadotropic hypogonadism and anosmia). The latter two processes have genes with large deletions that map to the Xp22.3 location.

X-linked ichthyosis is due to a genetic disorder of keratinization leading to a retention of scale. It is caused by a deficiency of the STS enzyme resulting from abnormalities in its coding gene. The STS gene is mapped to the distal part of the short arm of the X chromosome, specifically Xp22.3. 90% of X-linked ichthyosis patients have a complete deletion of the gene and 10% have a point mutation or partial deletion of the STS gene. One case in the literature reported a patient with somatic and germline mosaicism of the STS gene in a carrier and offered DNA slippage as the possible mechanism for this mosaicism. The origin of the X chromosome with the deletion of the STS gene was shown to be the grandfather of the proband.

STS is a membrane bound microsomal enzyme capable of hydrolyzing sulfated steroid hormones and cholesterol sulfate. Its activity is usually measured with dehydroepiandrosterone sulfate (DHEA) as a substrate. It is present in many tissues including the placenta, liver, kidneys, adrenals, ovaries, fibroblasts, epidermal cells, leukocytes, hair bulbs and testicular tissue. This enzyme normally has increasing activity at the stratum corneum-granular layer junction where it hydrolyzes cholesterol sulfate and sulfated steroid hormones. In normal epidermis, cholesterol sulfate decreases from 6% in the granular layer to 3% in the stratum corneum. In patients with X-linked ichthyosis, the STS deficiency results in levels of cholesterol sulfate in the stratum corneum approaching 12-30%. This increase in cholesterol sulfate along with decreased cholesterol in the stratum corneum leads to persistent keratinocyte adhesion and abnormal desquamation.

The measurement of STS levels differentiates X-linked ichthyosis from other ichthyosis types and identifies X-linked ichthyosis carriers. The enzyme is normally produced by the placenta where sulfated steroid precursors are converted to estrogens during pregnancy. A deficiency leads to low estrogen levels and difficulty initiating labor or slowed labor leading to a higher number of women requiring Cesarean sections, especially in primiparas. The course of pregnancy and fetal development appear to be normal except for skin findings in the newborn.

The histopathology of X-linked ichthyosis is nonspecific but typically shows mild to moderate compact orthokeratosis, a normal to thickened granular layer, and mild to moderate acanthosis. Ultrastructurally, an increased number of keratohyaline granules and desmosomes persist into the stratum corneum along with increased numbers of melanosomes which may account for the dark coloration of scales.

The main differential diagnoses of X-linked ichthyosis include other hereditary disorders of cornification such as ichthyosis vulgaris, lamellar ichthyosis, congenital ichthyosiform erythroderma and bullous ichthyosiform erythroderma. Distinction of the disorders of cornification is based on family history, onset and course of the disease, cutaneous findings, noncutaneous manifestations and histopathology. It is important to remember that climatic conditions can modify skin manifestations in ichthyosis complicating the diagnosis.

Ichthyosis vulgaris is the most common ichthyosis and affects 1 in 250 newborns or 1% of the population. It has autosomal dominant and appears in the first month of life with fine, white scales over the extensors, with flexural and intertriginous sparing, keratosis pilaris, atopy and palmoplantar hyperkeratosis and hyperlinearity. In X-linked ichthyosis these features are not seen. It generally improves with age whereas X-linked ichthyosis worsens with age. On histopathology, mild to moderate compact hyperkeratosis with a decreased or absent granular layer reflecting decreased or absent filaggrin, is important in making the diagnosis. This disorder is due to retention of scale. The genetic cause in ichthyosis vulgaris seems to be a keratohyaline defect that may affect the matrix protein of the stratum corneum.

The clinical distinction between X-linked ichthyosis and ichthyosis vulgaris may be difficult because they share many clinical features although they arise from different genetic defects. Overlap is frequent making the diagnosis challenging. Wells and Jenning reported specific diagnostic criteria used to differentiate ichthyosis vulgaris from X-linked ichthyosis. These included: family history of ichthyosis, age of onset, cutaneous manifestations (color and size of scales, site of maximal involvement and presence of palmoplantar involvement), ocular involvement and histopathology.

In a paper reported by Cuevas-Covarrubias, a sample of 66 unrelated Mexican patients with ichthyosis was studied. Clinical criteria included familial pedigree, age of onset, affected areas of the skin, characteristics of scale, and associated features. Assays of STS activity in leukocytes and amplification of the 5’3’ ends of the STS gene using PCR were performed. Patients all had similar distribution of scaling and two were classified as ichthyosis vulgaris due to atopy and palm-sole hyperlinearity yet proved to be X-linked ichthyosis by assays. According to the authors, atopy and palm-
sole hyperlinearity should not be trait specific for ichthyosis vulgaris nor should they exclude the possible diagnosis of X-linked ichthyosis. These results emphasize the use of laboratory studies to definitively confirm X-linked ichthyosis as a diagnosis. Using STS activity, X-linked ichthyosis may be differentiated from ichthyosis vulgaris by the enzymatic activity being absent.3

Other considerations in the differential diagnosis include lamellar ichthyosis which is autosomal recessive and presents as a collodion baby at birth. Later, large quadrilateral plate-like scales involving flexures, palms and soles develop. There is an increased incidence of ectropion. On histopathology severe compact hyperkeratosis with a normal granular layer is seen. This is a retention ichthyosis due to mutations in the gene encoding the enzyme transglutaminase.2

Congenital ichthyosiform erythroderma is also autosomal recessive and presents as a collodion baby at birth. Fine, white scales are seen over the entire body, with erythroderma, and increased alopecia. It is also due to a transglutaminase 1 deficiency. On histopathology moderate compact hyperkeratosis, focal parakeratosis, and a normal granular cell layer or diminished granular cell layer under parakeratosis are seen.3

Bullous ichthyosiform erythroderma is an autosomal dominant inherited disorder which presents in a neonate with erythroderma, scaling and bullae at birth and progresses to intertriginous verrucous, large and dark scales over time. On histopathology it shows compact hyperkeratosis, variable parakeratosis, vacuolization of the granular and upper spinous layers, and hypergranulosis with irregular and large keratohyaline granules. Abnormalities of the intermediate filament proteins keratin 1 and 10, and tonofilaments associated with desmosomes lead to acantholysis.2

There are a number of ways to confirm the diagnosis of X-linked ichthyosis. These include demonstrating gene deletion, lack of STS enzyme activity or increase in STS substrate. A FISH study may be performed from peripheral blood using a STS probe. Absence of the hybridization signal indicates a microdeletion of the STS gene. A STS assay shows reduced or absent enzyme activity in leukocytes, skin fibroblasts and keratinocytes in affected patients and to a lesser degree in carriers. Elevated cholesterol sulfate levels in the serum of affected patients can be detected by chromatography or spectrophotometry but serum cholesterol is normal in these patients. Lipid thin layer chromatography demonstrates increased cholesterol sulfate in the stratum corneum. Lipoprotein electrophoresis may also be used since increased cholesterol sulfate increases the electrophoretic mobility of low density lipoproteins. Additional methods for diagnosis include amplification of the 5’ 3’ ends of the STS gene using PCR because most of the patients have a complete deletion of this gene.4-6 Maternal urine can be used to detect high levels of sulfated estrogen precursors and low levels of estriol. Amniotic fluid analysis may be used prenatally to measure placental sulfatase activity and elevated DHEAS, a STS substrate.4

**Treatment**

The aim of treatment for X-linked ichthyosis is prevention and elimination of scales. Topical keratolytics such as ammonium lactate contain lactic acid, an alpha hydroxy acid with keratolytic action which results in disadhesion of corneocytes. Other treatments include emollients, hydrating agents, and topical retinoids. Lubrication and emollients which may soften the skin and preparations containing salicylic acid may provide help by removing the scales but results are typically unsatisfactory. Systemic retinoids may be effective but are only used in the most severe cases.

The bioactive form of vitamin D3 has been shown to modulate epidermal proliferation and differentiation. Calcipotriol is a synthetic vitamin D analogue with the capacity for binding to the vitamin D receptor and stimulating epidermal differentiation. A study by Kragballe et al used calcipotriol ointment versus placebo twice daily for 12 weeks in patients with disorders of keratinization. They concluded that short term treatment (12 weeks) of calcipotriol ointment up to 100g/wk is moderately efficacious, well-tolerated and safe in adult patients (over 12) with various ichthyoses. Although the study was limited to 67 patients with various ichthyoses, the authors suggested the possible investigation of combination therapy with calcipotriol and retinoids to observe potential synergistic effects and investigate their benefit.2

Topical tacalcitol (1α, 24-dihydroxyvitamin D3) has been tested in Japan as an alternative treatment for ichthyoses with retentive hyperkeratosis. In one single-blinded study of 9 patients by Okano, the medication failed to show effectiveness against different keratinizing disorders such as X-linked ichthyosis, ichthyosis vulgaris and acquired ichthyosis.7

This patient was successfully treated with ammonium lactate 12% cream once or twice per day and showed significant improvement in clinical scaling.

Certain consultations may be of benefit when working up a patient suspected of having X-linked ichthyosis. A urology consultation is important to evaluate for cryptorchidism or other genital abnormalities. An ophthalmology consultation may identify corneal opacities. In the case of delayed labor in a mother with a previous born X-linked ichthyosis child, an obstetrician or geneticist consultation for higher risk delivery in future pregnancies may be warranted.

**Conclusion**

X-linked ichthyosis is usually a clinically mild eruption due to a genetic disorder of keratinization. It develops at birth or in early infancy and may be associated with extra-cutaneous manifestations. Patients may present at a later age, as in our case, with complaints of dry skin. The condition is caused by a deficiency of STS that result from abnormalities in its coding gene. A lack of this enzyme results in increased levels of cholesterol sulfate. Accumulation of cholesterol sulfate is believed to cause persistent keratinocyte adhesion, which manifests as abnormal desquamation. Diagnosis is made in a variety of ways and treatment is directed towards the prevention and elimination of scales. The patient in this case presentation responded well to topical keratolytics applied once or twice a day.

**References:**


Case Report

The patient is a 68 year old Caucasian male who presented to the office complaining of a growth on his right lower leg that had been increasing in size for the last 3 months (Figure 1). He denied any pain or pruritus with the lesion and he denied a personal and family history of skin cancer. His medical history was significant for coronary artery disease, valvular heart disease, and previous strokes. His medications included warfarin, clopidogrel, metoprolol, losartan, hydrochlorothiazide, nitroglycerin, and ezetimibe.

On physical examination, the patient appeared to be well nourished and fully alert and oriented. The lesion in question was a solitary, round, hyperpigmented, fibrous 1 cm nodule located on the lateral aspect of the proximal third of his right lower leg. The differential diagnosis included neurofibroma, dermatofibroma, dermatofibrosarcoma protuberans, and nodular basal cell carcinoma and a shave biopsy was performed.

Findings on histopathological examination revealed a neoplasm within the dermis characterized by irregular aggregates of cells dissecting between collagen bundles and within blood vessels. The cells had large nuclei with minimal cytoplasm and nucleoli that were not conspicuous. The differential diagnosis at this point included metastatic neuroendocrine carcinoma and MCC. Immunohistochemical studies were performed and the neoplasm stained positively with antibodies against pankeratin, cytokeratin (CK) 20, synaptophysin, and CK 7. Further immunohistochemical studies with antibodies against endothelial cells failed to reveal vascular invasion.

A search for a primary occult lesion as the possible source of metastatic disease was undertaken and the patient underwent positron emission tomography (PET) scanning and gastrointestinal evaluation with colonoscopy which were all negative. The patient was then referred to a surgical oncologist for treatment. The lesion was treated as a primary malignancy and wide excision with sentinel node biopsy was performed.

Literature Review:

First described by Frederick Merkel in 1875 and by Toker in 1972 as a “trabecular cancer”, MCC is now considered to be the most aggressive cutaneous malignancy.1,2 Over 400 cases are reported each year in the United States with mortality rates between 25-35%.3,4 Merkel cells are of neuroendocrine origin and are found in the basal layer of the epidermis.5 They are believed to be slow acting mechanoreceptors that provide information about touch and hair movement.1 In the neoplastic form, they are considered a malignancy of the amine precursor uptake decarboxylase (APUD) system.2 Names synonymous with MCC of the skin include trabecular carcinoma, cutaneous APUDoma, primary small cell carcinoma, and primary neuroendocrine carcinoma.2

Epidemiology

MCC is a rare form of cutaneous skin cancer with an incidence of approximately 0.23/100,000 in whites with most cases occurring in the seventh decade of life.1 The incidence for blacks is one-twentieth of that for whites.1,4 Higher risk patients include those with congenital ectodermal dysplasia, Cowden’s disease, Hodgkin’s disease, chronic lymphocytic leukemia (CLL), and immunosuppression.1,4 Specifically, renal transplant patients have a risk of 0.13/1,000 while HIV patients have a relative risk of 13.4%.1

Clinical Presentation:

MCC usually presents as an asymptomatic red or violaceous papule or nodule. Surface features may include a shiny appearance, telangiectasia, and ulceration.1,3 They are often no larger than 2 cm in diameter on presentation and may have satellite lesions occurring secondary to lymphatic spread.1

Histology:

MCC occurs most often in the dermis and can extend into the subcutis. The basophilic tumor cells are small and monomorphic with round to oval shaped nuclei and scant cytoplasm.5,6 The triad of vesicular nuclei with small nucleoli, abundant mitoses, and apoptosis strongly suggests MCC.5 The Azzopardi phenomenon refers to the deposition of DNA around intratumoral blood vessels and has been reported in MCC.5

There are three main histological patterns of MCC - trabecular, intermediate, and small cell variant. The trabecular subtype is the least common pattern and iden-
Staging is based on the size of the primary tumor, nodal involvement, and metastasis (Table 2). Stage I accounts for 70-80% of cases, stage II 10-30%, and stage III 1-4%.

**Elective lymph node dissection (ELND)** is recommended in the absence of clinically positive nodes for high risk patients characterized by lesions greater than 2 cm, high mitotic rates (more than 10 mitoses per high power field), histological evidence of lymphatic permeation, and small cell histological patterns. For areas with indeterminate lymphatic drainage (i.e. tumors on the back), sentinel lymph node biopsy is recommended over ELND.

**Differential Diagnosis:**

The differential diagnosis of MCC includes basal cell carcinoma (BCC), melanotic melanoma, SCC, and cutaneous lymphoma.

**Treatment:**

Stages I and II are treated for curative intent while treatment of stage III is palliative. In stage I localized disease, acceptable treatment is achieved with wide excision and radiotherapy. Recent studies have indicated that optimal treatment is achieved via Mohs surgery with adjuvant radiotherapy. One study showed that patients treated with wide excision had a recurrence rate of 32%, whereas those treated by Mohs had a recurrence rate of only 8%. However, in cases where Mohs surgery may require a large excision, radiotherapy, as an adjunct to wide excision may be sufficient as the tumor is exquisitely radiosensitive. Acceptable margins for excision of a primary tumor is 2.5 to 3 cm though some suggest that smaller margins may be taken in cosmetically sensitive areas as long as radiotherapy is given. However, if no radiotherapy is given, wide margins are required for better survival.

Radiation therapy has been shown to reduce recurrences from 39% to 26% and regional failure (nodal metastasis) from 46% to 22%. Radiation therapy is started at 45-50 Gys in 20 to 25 divided fractions as soon as the excisional wound heals.

Stage II disease is treated with wide local excision of the primary tumor and regional lymph node dissection. If necessary, radiation at doses of 50-60 Gys are used to debulk nodal masses. Surgery is tailored to the patient and is based on the size and location of the nodes and the condition of the patient. The Trans-Tasman Radiation Oncology Group (TROG) treated 53 high risk patients with synchronized chemoradiotherapy and adjuvant chemotherapy which resulted in a three year survival of 76%. The role of chemotherapy in the treatment of MCC, however, still remains elusive.

Stage III disease occurs in 28-70% of patients at initial presentation. In patients with good bone marrow reserve and renal function, the platin agents, carboplatin and etoposide are favored and have resulted in 44% of patients having a complete response to therapy and 11% having a partial response. Other studies have shown this combination to have a 60% response rate compared to the cyclophosphamide, oxorubicin (or epirubicin), and vincristine combination which has shown a 75.5% response rate. Further studies are required. In addition, for those patients with ulcerating, bleeding, or fungating masses, radiation therapy can be used palliatively.

**New Treatments:**

Nerve growth factor inhibitor and Bcl-2 antisense oligonucleotides are the newest chemotherapeutic agents presently being studied. However, with reports of spontaneous remission even in stage III disease, research is focusing more on immunotherapy.

**Prognosis:**

Poor prognostic signs include nodal disease (median survival is 13 months vs. 40 months if nodes are not involved), metastasis (median survival 9 months), male sex, tumor size greater than 2 cm, age older than 60 years, and lack of radiotherapy. The prognosis of lesions in the lower extremities may also be relatively poorer since these lesions are often under treated because of less tolerance to radiation and greater difficulty in repairing wide excisions in this site.
Recurrence:
Local recurrence occurs in approximately 20-44% of patients within 4 months of excision. Regional lymph node dissection and radiation therapy are options for these patients and those who have reached their maximum tolerated dose of radiation or have had complete nodal dissection. For patients who can neither have further radiation or nodal dissection, chemotherapy may be an option.

Follow-up:
Patients diagnosed with MCC should be followed closely with visits every 3 months for the first three years followed by annual appointments. Each visit should consist of a full detailed physical exam and a review of systems. Laboratory and radiological studies are ordered when clinically warranted.

Conclusion:
Merkel cell carcinoma, although a rare neoplasm, must be considered in those patients with risk factors because of its aggressive behavior. Its relatively benign clinical appearance can often delay diagnosis and increase the likelihood of local spread and metastasis. A high index of suspicion is required and a biopsy, at the very least, is warranted for these unassuming lesions especially in elderly patients complaining of a rapid growth on sun exposed skin areas.

References:
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Unilateral Laterothoracic Exanthem-A Case Report

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ABSTRACT

Unilateral laterothoracic exanthem (ULE), also known as asymmetric periflexural exanthem of childhood (APEC), is a disease of probable viral origin characterized by unilateral onset and predictable progression. The disease was first described in 1962 by Brunner in a paper entitled, “A new papular erythema of childhood” (1). Thirty years later, Bodemer and Prost described 18 patients with a similar unilateral rash and named the disease Unilateral Laterothoracic Exanthem (2). Case reports concur that onset is always unilateral and frequently localized to the axilla, laterothoracic region and flank. The rash commonly progresses in a centrifugal pattern, becoming bilateral while maintaining an asymmetric appearance. A 12 month old male presented to our office with scattered, mildly erythematous, scarlatiniform papular lesions on the left arm, left thorax, left leg and left palm. With the existence of so many nonspecific viral eruptions in childhood, the subjective report of unilateral onset is often times the clinicians’ key to diagnosis.

Introduction

Historical Perspective

Prior to receiving its name, unilateral laterothoracic exanthem was first described in 1962 by Brunner et al in a paper entitled, “A new papular erythema of childhood”. They spoke of a newly described, erythematous eruption, primarily unilateral, noted in children between the ages of 6 months and 5 years.1 Similar unilateral lesions were independently reported by Dr. William Laur in the same year during a dermatology presentation at the 1962 Texas Medical Association meeting. He described 175 patients with a patch of discrete, papular, pink, lichenoid lesions often appearing on one side of the thorax and extending into the axillary region. He proposed the name lichen miliaris.3 Thirty years later in 1992, Bodemer and Prost coined the term Unilateral Laterothoracic Exanthem (ULE) to describe the disease. They described eruptions in 18 children, initially unilateral and localized close to the axilla, which had characteristic features.5

Definition

Unilateral laterothoracic exanthem is a disease of unknown etiology occurring primarily in children between 6 months and 5 years of age and identifiable by its distinct eruptions with unilateral onset.

Etiology

Unilateral laterothoracic exanthem has no known cause but is speculated by some investigators to have a viral etiology.2 The disease affects girls more commonly than boys (2:1) and usually occurs in late winter and spring. Duration of illness varies significantly from case to case but has been reported to last anywhere from 2 weeks to 12 weeks. The illness resolves spontaneously without treatment.

Clinical Description

Lesions most commonly arise on the trunk or axilla but in rare cases may begin on the extremities or in the groin region.4 Regardless of initial localization, eruptions ultimately will advance to involve the thorax.7 Spread is centrifugal with approximately 70% of cases advancing to the contralateral side.6 The eruptions maintain an asymmetric appearance throughout the disease course with the side of onset being dominantly affected. Involvement of the hands, feet and face, although rare, has been noted.7

Eruptions are usually small erythematous papules, scarlatiniform in appearance but poorly demarcated.8 Initially morbilliform in nature, these mildly pruritic lesions progress to eczematous plaques.4 A distinct halo surrounding the papules is considered by some researchers to be a key diagnostic feature.1,4

Histologic Description

Skin biopsies show mild to moderate perivascular, predominately lymphocytic, infiltrate composed primarily of T lympho-
Scattered, mildly erythematous, scarlatiniform papular lesions were observable unilaterally on the left arm (figure 2), left lateral thorax extending to the left flank, left leg and left palm. The left side was largely affected but the right was spared. Affected areas had atopic appearing skin.

Follow up examination revealed complete resolution of the unilateral laterothoracic exanthem. Total disease duration was four weeks with spontaneous resolution.

Discussion

Although the etiology of unilateral laterothoracic exanthem is unknown, the proposed theories of viral origin seem appropriate. Viral exanthems are very common in childhood and most often harmless. The young age of the affected population, its seasonal affliction, and its associated viral symptoms like lymphadenopathy, upper respiratory tract infections and fever are all suggestive of a viral cause. In addition, researchers report broad spectrum antibiotics to be an ineffective treatment. Spontaneous resolution without the aid of steroids, creams, antibiotics, or antihistamines is inevitable although the extensive variability of time course makes complete resolution unpredictable. No long term recurrences have been reported.

The term unilateral laterothoracic exanthem can be misleading. Although the unique distinction of this disease is its obvious onset on one side of the body, the diagnosis is commonly missed. Often times children do not present to the practitioner until the rash has significantly spread. With as many as 70% of the cases having bilateral involvement, the likelihood of a child presenting with a nondistinct bilateral rash is very high. A good history, revealing unilateral onset, and a high index of suspicion are often necessary to accurately diagnose unilateral laterothoracic exanthem. Unilateral laterothoracic exanthem typically spares the face, hands, feet and genitals although rare cases involving these areas have been reported.

In our patient, the characteristic unilateral onset, age, seasonal predominance, rash appearance and clinical features were observed. The lesions remained unilateral throughout the entire four week duration of the illness.

Conclusion

The differential diagnosis for unilateral laterothoracic exanthem includes many common skin eruptions. Among others, it is not uncommon for unilateral laterothoracic exanthem to be mistaken for scabies, atopic dermatitis, tinea corporis, or scarlet fever. Although all are very treatable, each entity has its own distinctive treatment regimen and time course. With a definitive diagnosis of unilateral laterothoracic exanthem, parents can avoid using unnecessary prescriptions and be assured of the illness’ harmless nature and spontaneous resolution. It is likely that the incidence of unilateral laterothoracic exanthem is much higher than what is currently reported in the literature. Although it is considered a harmless illness, the importance to differentiate it from other viral exanthems of childhood will accumulate significance as we learn more about its etiology.

References:

**Safety Information**

The most commonly reported side effects were headache, burning at the application site, and nasopharyngitis. The cause of potential optic axis suppression. Treatment should not exceed two weeks or grams per week to prevent visible optic axis suppression. May occur with potential glucocorticoid insufficiency after withdrawal of treatment. Long-term treatment demonstrated optic axis suppression in two out of adults. This should not be used on the face, groin, or axillae in patients under years or for the treatment of rosacea or perioral dermatitis.

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Fluocinonide is a corticosteroid that is used topically as an anti-inflammatory and antipruritic agent. It is an almost odorless white to creamy white crystalline powder that is practically insoluble in water and slightly soluble in ethanol.

Corticosteroids constitute a class of primarily synthetic steroids used topically as anti-inflammatory and antipruritic agents.

**Pharmacokinetics**

The extent of percutaneous absorption of topical corticosteroids is determined by many factors. The primary measure of efficacy was the proportion of patients whose psoriasis lesions cleared or almost cleared at the end of treatment. Results are presented in the table below as patients cleared or almost cleared at 7 weeks with once or twice-daily application.

**Contraindications**

Fluocinonide is contraindicated in those with a history of hypersensitivity to any of the components of the preparation.

**Adverse Effects**

Other adverse events were reported by more than one subject receiving active treatment. The incidence of all adverse events was:

- 5% or more: 1.6% with once-daily application
- 1% to 4.9%: 0.7% with twice-daily application
- 0.1% to 1.9%: 0.3% with once-daily application
- Less than 0.1%: 0.1% with twice-daily application

**Dosing**

Fluocinonide is supplied in aluminum tubes as follows:

- 0.5% w/w: 14 g per tube
- 0.05% w/w: 14 g per tube
- 0.1% w/w: 14 g per tube
- 0.2% w/w: 14 g per tube

For children under 2 years of age, the total dose should not exceed 0.5 mg/kg/day and the duration of treatment should not exceed 2 weeks. For children 2 years of age and older, the total dose should not exceed 2 mg/kg/day and the duration of treatment should not exceed 4 weeks.

**Precautions**

While on treatment, more than one topical corticosteroid-containing product at the same time may cause systemic absorption and produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, which may not be reversible for weeks after the drug is stopped. Furthermore, topical corticosteroids are not recommended for facial use.

**Interactions**

Topical corticosteroids may cause systemic absorption and produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, which may not be reversible for weeks after the drug is stopped.

**Pregnancy and Nursing**

Fluocinonide should not be used for any disorder other than that for which it was prescribed.

**Other**

Pregnant or lactating females should consult their healthcare provider before using this medication.

**Legal Information**

This is not a complete list of all possible side effects. If you have any questions about the side effects, consult your healthcare provider.
Hair follicles

The role of androgens in

Estrogen acts via estrogen

that determine when the follicle undergoes
papilla have many signaling interactions
region. The stem cells and the follicular
are believed to be located in the bulge
which the hair is shed. Since the hair follicle
remains quiet until the end of the phase in
the lower portion of the hair follicle under-

Hormonal Controls of Hair: What is the Role of Menopause?

Women currently spend one-third of their lives in a post-menopausal state. The significant hormonal alterations that occur
during menopause cause many changes throughout the body, including the skin. Various lines of evidence suggest that modifi-
cations in hair growth and texture may also occur in post-menopausal women; however these changes have not been carefully
examined.

When evaluating and treating a post-menopausal woman with hair loss, it is crucial that the clinician understand the role of
hormones in hair growth and cycling. To that end, this article reviews the current body of knowledge on hormonal hair controls,
and addresses the possible ramifications of hormonal changes in post-menopausal hair

Background

Embryology and Anatomy: Hair follicles are first seen in the ninth week of gestation
with no new hair follicles formed after birth. The normal scalp contains roughly 100,000
hairs. Each hair follicle is typically divided
into three sections: the infundibulum, isthmus,
and the lower follicle. The infundibulum
extends from the skin surface to the
opening of the sebaceous duct. The isthmus
extends from the sebaceous duct to the
insertion of the erector pili muscle. Finally,
the lower follicle extends from the
muscle to the base of the matrix. The
matrix surrounds the follicular papilla,
which is the capillary-containing dermal
structure.

Hair Cycle: Hair cycling consists of three
stages: growing (anagen), involution (cata-
gen), and resting (telogen). During the anagen
stage, the matrix cells proliferate and
produce hair shaft. It is estimated that
about 90% of hair follicles located on
the scalp are in the anagen phase. Cata-
gen phase is a state of regression in which
the lower portion of the hair follicle under-
goes resorption as it moves upward to the
level of the hair bulge. Finally, telogen is
the resting phase in which the follicle
remains quiet until the end of the phase in
which the hair is shed. Since the hair folli-
cle is a self-renewing tissue, stem cells are
present for regeneration. These stem cells
are believed to be located in the bulge
region. The stem cells and the follicular
papilla have many signaling interactions
that determine when the follicle undergoes
cyclic transformation.

Menopause: Menopause is defined as
the permanent cessation of menses. The
mean age that women undergo menopause is 51 thus women spend about
one-third of their life in the post-
menopausal period. The post-menopausal
ovary produces minimal estrogen. The
major source of estrogen in the post-
menopausal female is from adrenal andro-
gen, which undergo aromatization by

Peripheral Tissues to Estrogens:

Women who chose to begin hormone replacement
therapy typically take estrogen alone or in
combination with progestin. Hormone replacement therapy is known to relieve
menopausal symptoms and physical
changes associated with depleted endoge-

Hormonal Controls of Hair

Androgens: The role of androgens in
hair growth and cycling has been well
described. The growth of human hair,
except for the scalp and eyelashes, is
increased by androgens as is the diameter
and length of the hair fiber. The duration
of the anagen cycle is also lengthened by
androgens resulting in hairs becoming
longer. However androgens are also para-
doxically involved in scalp hair thinning in
hereditary or androgenetic alopecia.

Androgens are derived from three
sources: gonads, adrenal gland, and the
peripheral conversion of weak precursor
hormones into potent androgens. Within
certain cells, dehydroepiandrosterone and
androstenedione may be converted to
testosterone, and testosterone may be
converted to the move potent androgen
dihydrotestosterone (DHT). The conver-
sion of testosterone to 5-alpha-dihy-
drotestosterone (DHT) can occur by two
distinct isoforms of 5 a reductase-type I
and type II. Both type I and type II isoen-
zymes have been identified in the outer
root sheath of hair follicles of men and
women. Unbound circulating androgens
diffuse into cells where they bind directly to
intracellular androgen receptor or after
conversion to DHT. These receptors then
behave as transcription factors that can
stimulate or inhibit gene expressions by
binding to DNA hormone response ele-

Several clinical observations have sup-
ported the role that androgens are involved
in the hair cycle. It has been noted since
ancient times that men castrated before
puberty retain their prepubertal hairline and
do not go bald. Patients with mutations in
the 5-alpha-reductase II gene, do not expe-
rience recession of the hairline or balding.
Also, it has been shown that 5-alpha-
reductase type II inhibitor, finasteride,
resulted in halting the progression of bald-
ing in men. These observations support
the theory that DHT, the potent metaboli-
testosterone, may convert large follicles
to miniaturized follicles in specific regions
of the scalp. Hair transplantation demon-
strates that hair follicles from the occipital
scalp are affected very little by androgen-
mediated hair miniaturization unlike the
hair follicles located on frontal area of the
scalp. After transplantation to the frontal
scalp, the occipital hairs continue to grow
proving that androgen responsiveness is
determined at the level of the follicle.
Since the diameter of the hair correlates
with volume of the dermal papilla, andro-
gens must mediate their effect by affecting
the dermal papilla. In fact, two studies on
human skin have shown androgen recep-
tor expression in the nuclei of cells in the
dermal papilla. In another study it was
noted that both women and men have
higher levels of androgen receptors in the
frontal hair follicles than in occipital
follicles.

Estrogen: Estrogen acts via estrogen
receptors that belong to a superfamily of
nuclear receptors. There are two known
estrogen receptors termed alpha (ER
alpha) and beta (ER beta). Several stud-
ies have demonstrated the influence of
estrogen on the rodent hair cycle. For
example, Smart and colleagues have
shown that placing topical estradiol on
mice maintains their hair follicles in telogen
phase thus blocking its movement into
anagen, resulting in the inhibition of hair
growth. Furthermore, the application of an
antiestrogen stimulated the telogen follicle

into anagen earlier than the control mice. Thus the effect of estrogen may be due to an inhibition of the telogen-anagen transition. Work performed by Johnson showed that the removal of ovaries in rats increased the growth and length of hairs, and accelerated the loss of club hairs. Treatment of the ovariectomized rats with estradiol reduced the rate of growth and delayed the loss of the telogen club hair suggesting that estradiol can prevent the initiation of anagen and lengthen the duration of the resting period.

The follicular target for estrogens in rodents is mainly the dermal papilla with some localizations to the outer root sheath. A recent study performed by Moverare et al, suggested that the effect of estrogen on the hair cycle is via estrogen receptor alpha resulting in inhibition of telogen-anagen transition in mice. Immuno-histochemical stains have localized the ERα to the dermal papilla of telogen follicles.

Recently through the advances in tissue culture techniques, it has been shown that organ culture of human scalp hair follicles exposed to 5ng/ml of estradiol results in decrease growth. However, in the same study it was shown that the cells of the in the dermal papilla when exposed to similar levels of estradiol resulted in proliferation. Estrogen is clearly an important regulator of hair follicle cycling however its effects in humans are not fully known.

In pregnant women, estrogen an increase in hair growth due to a greater number of hairs in the anagen phase is seen. During the postpartum period, the excess anagen hairs may enter the telogen phase, resulting in a dramatic hair shedding. Although higher estrogen levels likely play a role in this alteration of hair cycle, it is difficult to attribute this phenomenon to estrogen alone because there are many hormonal changes seen in pregnancy such as increase in progesterone and prolactin.

Alterations in the hair cycle may also occur in postmenopausal women however the etiology of such changes is not well understood. To date, animal and human studies investigating the role of estrogens on the hair cycle have been conflicting. Chronic telogen effluvium is a recently described condition that results in diffuse scalp hair loss and is typically seen in women in their fourth to sixth decades of life. It typically presents with an abrupt hair loss that can have a fluctuating course lasting at least 6 months and may continue for 6-7 years. Chronic telogen effluvium is usually self-limiting, however the volume of hair typically does not return to premorbid volume.

Inflammatory hair disorders have also been described in post-menopausal women. A condition that is seen almost exclusively in post-menopausal women is frontal fibrosing alopecia. Frontal fibrosing alopecia is associated with perifollicular erythema and progressive frontal hairline recession and is considered a variant of lichen planopilaris. Frontal fibrosing alopecia is likely not the main cause of post-menopausal hair loss since it has been recently reported to occur in a man and hormone replacement therapy did not appear to alter the course of disease.

In summary, until further studies are carried out to better study the hormonal alterations in menopause and the effects they may have on the hair cycle there is inadequate information to attribute specific hair changes to hormonal alterations seen in menopause. There is currently no evidence to recommend hormone supplementation as treatment of any hair changes in a post-menopausal woman.

The practitioner seeing a post-menopausal woman with a complaint of hair loss needs to evaluate the woman for all possible causes while validating the possibility that hormonal alterations of menopause may influence the hair follicle.

References:
ABSTRACT

Cellulitis is a skin infection generally caused by gram-positive bacteria, which often travels into subcutaneous tissue. Although Staph. aureus and Strep. pyogenes are the most common culprits, a myriad of other organisms can cause this disease. While “common diseases are common,” it is crucial to determine the organism causing the disease in order to appropriately treat the patient.

Key Words: Cellulitis, Aeromonas, Flavobacterium

Case Report

This 52-year-old male presented with a two-year history of metastatic prostate carcinoma. He had received hormonal and chemotherapeutic treatments without significant response. The patient had a history of chronic back pain and a traumatic right above the knee amputation. He presented to the emergency department because of progressive vomiting and intractable pain due to bone metastases.

The patient had chronic lower extremity edema for several months prior to presentation. A few weeks prior to presentation, the patient experienced increased swelling and discoloration of his left leg. He denied fever or chills. He developed a erythematous and violaceous patch with a pale white central area. The patient was started on cephalexin (Keflex) for leg cellulites nine days prior to presentation. He began to have nausea and vomiting with decrease in his oral intake. The patient was unable to take his medications on a regular basis.

The patch on his left leg was noted on presentation. The patient had an abnormal BUN, creatinine, as well as being hypokalemic and hyponatremic. He was also hypotensive. A working diagnosis of cellulitis was entertained, and he was started on ampicillin/subbactam (Unasyn) in the emergency room. Piperacillin/tazobactam (Zosyn) was started after admission, and a tissue biopsy was also obtained. The routine culture displayed no preliminary growth. At 48 hours the routine culture exhibited oxidase positive catalase positive long thin gram negative bacilli. The anaerobic culture was negative at 72 hours as oxidase positive gram negative bacilli that fermented glucose. These organisms were ultimately identified as Flavobacterium spp. and Aeromonas spp. respectively. The AFB smear was negative.

The tissue biopsy was interpreted as containing basket weave orthokeratosis with underlying epidermal spongiosis and necrosis. There were no significant infiltrate in the subepidermal region noted, although subepidermal vesicle formation was noted. There were distended capillaries in the papillary and reticular dermis. Edema and hemorrhage were present.

Degeneration of sweat gland and hair follicle epithelium was seen in the deep portions of the reticular dermis with neutrophils, eosinophils, and mononuclear inflammatory cells scattered throughout. Pan cytokeratin and PSA immunohistochemical stains were performed to exclude metastatic prostate carcinoma based on the patient history. Both stains were negative. The diagnosis of cellulitis was established based on the clinical and histological appearance.

The patient’s therapeutic regimen was modified to ciprofloxacin, to which both organisms were sensitive to, with a MIC of <=0.5. Blood cultures remained negative after five days. Following a brief hospital stay, the patient was discharged on ciprofloxacin, pain medications, outpatient nursing care, and other palliative measures.

Discussion

The suppurative, erythematous inflammation of cellulitis can occur in any area of the body. There are many organisms that cause cellulitis (Table 1). The differential diagnosis for cellulitis includes erythema nodosum, erythema gangrenosum, insect bites, dermatitis, or Well’s syndrome.1 The skin margins of cellulitis are usually poorly demarcated, except for erysipelas, which has sharply demarcated borders. The erythematous region may become nodular and vesicular, which can rupture to reveal pyogenic and necrotic material (Table 2).2 The disease may involve males more than females and more commonly involves the lower extremities.2 There are risk factors associated with developing cellulitis, specifically sites of entry (trauma, intertrigo), venous insufficiency, peripheral edema, lymphedema, tinea pedis, and obesity.3,4 Complications resulting from cellulitic infec-
tions include gangrene, metastatic abscess, bacteremia, and sepsis.1 In most cases, cellulitis is diagnosed by skin appearance alone, as cultures of the site are not easily obtained. However, not utilizing culture and sensitivity techniques to pinpoint the offending organism, may occasionally result in ineffective treatment. Particularly when unusual organisms are involved.

Aeromonas spp. are oxidase-positive, glucose-fermenting, facultative anaerobic gram-negative bacilli. They are isolated primarily from water sources (chlorinated and non-chlorinated) and foods such as meat and fish. Infections appear to become more prevalent in warmer months.7 Virulence factors for this organism are listed in Table 3.8 Aeromonas spp. have been associated with various human infections including cellulitis, bacteremia, sepsis, and gastroenteritis. About 25 -100% of isolated species are beta-lactam resistant, which may be problematic in treatment, limiting available options.8 Quinolones are the drug of choice, but resistant strains may also be susceptible to TMP-SMX and tetracyclines.9,10

In our patient, cellulitis was caused by two less common organisms, which had resistance to multiple antibiotics. This case illustrates the value of obtaining a culture and sensitivity. In the setting of an immunocompromised patient, to help direct effective antibiotic therapy. Cultures should be considered in settings where the patient is immunocompromised, there are open wounds, or when response to initial antibiotic therapy is not optimal. Punch biopsies can be helpful for obtaining a microbiologic diagnosis.8

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17. Di Pentima MC, Mason EO Jr, Kaplan SL. In vitro antibi-
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<table>
<thead>
<tr>
<th>Table 1. Examples of Various Etiologies of Cellulitis</th>
</tr>
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<tbody>
<tr>
<td>Staph. aureus</td>
</tr>
<tr>
<td>Strep. pyogenes</td>
</tr>
<tr>
<td>group B, C, G strep.</td>
</tr>
<tr>
<td>Erysipelothrix Rhusiopathise</td>
</tr>
<tr>
<td>Pneumococcus</td>
</tr>
<tr>
<td>H. influenza</td>
</tr>
<tr>
<td>E. coli</td>
</tr>
<tr>
<td>C. jejuni</td>
</tr>
<tr>
<td>Moraxella</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
<tr>
<td>Cryptococcus neoformans</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
</tr>
<tr>
<td>Vibrio spp.</td>
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</table>


<table>
<thead>
<tr>
<th>Table 2. Resident/Systemic Findings Characteristic of Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resident</strong></td>
</tr>
<tr>
<td>Macular erythema</td>
</tr>
<tr>
<td>Nodules and/or vesicles</td>
</tr>
<tr>
<td>Generalized warmth and tenderness</td>
</tr>
<tr>
<td>Regional lymphadenopathy</td>
</tr>
<tr>
<td>Abscess development</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Leukocytosis</td>
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<td>Myalgias</td>
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<th>Table 3. Virulence Factors for Aeromonas spp.</th>
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<tbody>
<tr>
<td>Cytotoxic toxin</td>
</tr>
<tr>
<td>Capsule</td>
</tr>
<tr>
<td>Cytotoxic toxin</td>
</tr>
<tr>
<td>Adhesins</td>
</tr>
<tr>
<td>Proteases</td>
</tr>
<tr>
<td>Agglutinins</td>
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<tr>
<td>Hemolysins</td>
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<tr>
<td>Pili</td>
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<tr>
<td>Enterotoxins</td>
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<tr>
<td>Enzymes</td>
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<tr>
<td>Lipases</td>
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<tr>
<th>Table 4. Reclassification of Flavobacterium spp.</th>
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<tbody>
<tr>
<td>Flavobacterium meningosepticum</td>
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<tr>
<td>Chryseobacterium meningosepticum</td>
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<tr>
<td>Flavobacterium indologenes</td>
</tr>
<tr>
<td>Chryseobacterium indologenes</td>
</tr>
<tr>
<td>Flavobacterium odoratum</td>
</tr>
<tr>
<td>Myroides odoratus</td>
</tr>
<tr>
<td>Myroides odoratinimus</td>
</tr>
<tr>
<td>Flavobacterium multivorum</td>
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<tr>
<td>Sphingobacterium multivorum</td>
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<tr>
<td>Flavobacterium spirillum</td>
</tr>
<tr>
<td>Sphingobacterium spirillum</td>
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Introduction

"Testicular choriocarcinoma is a highly malignant germ cell neoplasm with an estimated incidence of 2 to 4 per 10 million and accounting for 0.01 to 0.02 percent of malignant disease in males". Initial symptoms may be testicular enlargement with or without pain. However, often times the tumor is not found until metastasis has occurred. Metastasis of choriocarcinoma is often to the lungs, liver and brain. Skin metastasis is very rare. In review of the literature, there are six cases of testicular choriocarcinoma with cutaneous metastasis (Table 1). We present the sixth case.

Case Report

Our case is a 20-year-old Hispanic man who was evaluated during a hospital admission for three lesions on his scalp of approximately three months duration. The patient’s mom stated that the lesions appeared abruptly and would bleed profusely after manipulation by the patient. The patient and his family had been told by his pediatrician that these were hemangiomas and he was scheduled to have them excised by a plastic surgeon three weeks after the date of our evaluation.

The patient had been admitted to the hospital two days prior with bilateral groin/testicular pain. His past medical history was significant for cerebral palsy and retractable testes. He was born at 26 weeks gestation due to premature rupture of the membranes. The patient was taking baclofen for muscle spasms. He had no known drug allergies.

Physical examination of the scalp revealed three glistening red ulcerated polypoid nodules measuring 0.5 cm, 0.8 cm and 1.0 cm (Fig. 1). Our initial impression was most consistent with pyogenic granulomas based on the patient’s history and on the fact that pyogenic granulomas have a propensity for multiple eruptions that may be localized or disseminated. However, the scalp is not a typical site for pyogenic granulomas. The most common sites for pyogenic granulomas include gingiva, fingers, lips, face and tongue. A shave biopsy of one nodule was performed. Pathologic exam revealed a very vascular tumor stroma with epidermal nests and sheets of large cells with predominantly clear cytoplasm and vesicular-appearing nuclei. Mitosis and multinucleated giant cells were present. Large multinucleated cells with basophilic cytoplasm were present in close association with cuboidal cells that exhibit pale cytoplasm (Fig. 2). Cytokeratins AE1/AE3 as well as human chorionic gonadotropin (HCG) strongly stained the tumor cells. Human placental lactogen (HPL) focally stained the tumor cells. Placental alkaline phosphatase (PLAP) and alpha-fetoprotein (AFP) stains were negative. The histologic diagnosis was metastatic malignant germ cell tumor consistent with choriocarcinoma.

Ultrasound of bilateral testes revealed multiple bilateral testicular masses. CT of the chest and MRI of the head revealed multiple metastatic lesions. Orchiectomy of the left testicle revealed a markedly atrophic testis with a mixed malignant germ cell tumor consisting of choriocarcinoma and teratoma. The tumor was predominantly choriocarcinoma, with extensive hemorrhage and necrosis, with a minor component (<5%) of teratoma. Pathologic exam of the choriocarcinoma revealed cuboidal cells with large vesicular nuclei surrounded by large multinucleated cells with basophilic cytoplasm (Fig. 3). The immunostain pattern was identical to the one obtained from the scalp metastasis: positive for cytokeratins AE1/AE3 and HCG, focally positive for HPL, and negative for AFP and PLAP. Orchiectomy of the right testicle revealed a markedly atrophic testis with a focus of seminoma.

Discussion

Choriocarcinoma is a germ cell tumor that arises from malignant transformation of trophoblastic cells that secrete human chorionic gonadotropin. Although usually a gestational tumor, choriocarcinoma may be derived from the testis, and more rarely, the mediastinum and ovaries. In women, the malignant tumor arises from fetal trophoblasts. Although the incidence is extremely rare, studies show that approximately half arise from hydatiform moles, 25 to 30 percent from previous abortions or ectopic pregnancies and 20

ABSTRACT

A case of cutaneous metastatic choriocarcinoma presenting as three glistening red ulcerated polypoid nodules resembling pyogenic granulomas on the scalp of a 20-year-old man with a history of cerebral palsy is reported. Histologic findings revealed two types of cells distinctive for choriocarcinoma, syncytiotrophoblasts and cytotrophoblasts. Staining of tumor cells was strongly positive for human chorionic gonadotropin antigen and cytokeratins AE1/AE3. Human placental lactogen focally stained the tumor cells. During the same hospital admission, histologic exam of the tumors from bilateral undescended testes revealed choriocarcinoma, seminoma and teratoma. Metastatic lesions were also found in the lungs and brain. The patient underwent bilateral orchiectomy, radiotherapy and chemotherapy but died four months after diagnosis.
Table 1. Review of the literature: Skin metastasis of testicular choriocarcinomas (1948-2003)

<table>
<thead>
<tr>
<th>Case (Reference)</th>
<th>Age</th>
<th>Clinical Features of Skin Metastasis</th>
<th>Location</th>
<th>Metastases other than skin</th>
<th>Other Germ Cell Tumor Present</th>
<th>Prognosis (survival time after skin metastasis found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (9)</td>
<td>24</td>
<td>“Firm bluish nodules…size of a small cherry….freely movable”</td>
<td>Scalp, abdomen, right inguinal fold and right calf</td>
<td>Lung, bilateral perihilar lymph nodes</td>
<td>None identified</td>
<td>Died (1 month)</td>
</tr>
<tr>
<td>2 (10)</td>
<td>Not identified</td>
<td>“small, round, firm…non-painful nodule”</td>
<td>Lip</td>
<td>Lung</td>
<td>Embryonal carcinoma</td>
<td>Died (2 weeks)</td>
</tr>
<tr>
<td>3 (6)</td>
<td>23</td>
<td>“violaceous nodule..3 cm…painless…itched”</td>
<td>Chest</td>
<td>Lung, brain, liver, para-aortic nodes</td>
<td>None identified</td>
<td>Alive (2 years)</td>
</tr>
<tr>
<td>4 (1)</td>
<td>23</td>
<td>“raised erythematous mass…firm”</td>
<td>Scapula</td>
<td>Lung, brain, liver, kidney</td>
<td>None identified</td>
<td>Died (10 days)</td>
</tr>
<tr>
<td>5 (2)</td>
<td>22</td>
<td>“multiple firm reddish nodules…slightly painful”</td>
<td>Upper back</td>
<td>Lung, brain, liver</td>
<td>Pure</td>
<td>Died (3 months)</td>
</tr>
<tr>
<td>6 *</td>
<td>20</td>
<td>“red ulcerated polypoid nodules”</td>
<td>Scalp</td>
<td>Lung, brain</td>
<td>Seminoma, Teratoma</td>
<td>Died (4 months)</td>
</tr>
</tbody>
</table>

* Present case.

percent follow normal pregnancies. In men, choriocarcinoma usually occurs as a component of a testicular mixed germ cell tumor. It occurs as a “pure” tumor in only 0.3 to 1.3 percent of all testicular neoplasms. However, in this review of the literature, choriocarcinoma was a component of a mixed germ cell tumor in only two cases, 2 and 6 (Table 1).

Choriocarcinoma is a tumor of trophoblastic tissue: the cytotrophoblast, the proliferative component and the syncytiotrophoblast, the hormonally active component. The cytotrophoblasts usually grow in clusters, and the cells appear cuboidal with large vesicular nuclei often with prominent nucleoli and pale cytoplasm. Mitotic figures may be conspicuous and are frequently abnormal. The syncytiotrophoblasts are composed of very large cells with abundant basophilic cytoplasm. They are frequently multinucleate and may be seen in intimate association with the neighboring cytotrophoblasts. The syncytiotrophoblasts are positive for human chorionic gonadotropin antigen. Identification as choriocarcinoma is dependent on the presence of syncytiotrophoblasts and the presence of hCG on immunostain.

In summary, this case was presented not only for interest, but also to reinforce the fact that histopathologic confirmation is important if presentation is atypical.

References:
How I did it...........

After resection of a tumor on the left medial eyebrow. Repair of the resulting defect while preserving the medial brow contour.

**Tumor:**
Basal Cell Carcinoma

**Procedure:**
Resection. Pathology for clear margins. Repair 48 hours later.

**Flap:**
Laterally Based Advancement Flap

---

**Figure 1**
Planned Resection

**Figure 2**
Resection

**Figure 3**
Lateral Brow Advancement

**Figure 4**
Immediate Closure

**Figure 5**
8 Days Post Op

**Figure 6**
12 Weeks Post Op
What *really* irritates me is acne medicine that doesn't deliver the results I want.

It's time for Tazorac®
The results are worth it.
Patients like the results.

- **Patients like the results in everyday clinical practice with TAZORAC® Cream 0.1%**: 
  - 77% increase in patient satisfaction at weeks 10–12 (n = 167)
  - 68% of patients reported they were satisfied/very satisfied at weeks 4–6 (n = 185)

- **Patients like the results in a double-blind clinical study with TAZORAC® Cream 0.1%**: 
  - 84% reported a highly favorable/favorable impression at week 12 (n = 76)
  - 76% rated acne severity as none/trace/mild at week 12—compared to only 33% at baseline (n = 76)

Patient treated with TAZORAC® Cream 0.1% once daily. Photographs are completely unretouched. Results may vary.

TAZORAC® Cream 0.1% is indicated for acne vulgaris.

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

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

Please see adjacent page for brief summary of prescribing information.

TAZORAC®
(tazarotene) Cream, 0.1%  

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

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

CONTRAINDICATIONS:  

- TAZORAC® Cream is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, treatment should be discontinued.
- TAZORAC® Cream is contraindicated in women who are or may become pregnant during lactation.
- TAZORAC® Cream is contraindicated in patients with known hypersensitivity to any of the components.

PRECAUTIONS:  

- Pregnancy:azzatorene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.
- Nursing Mothers: Tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans.
- Use in the Elderly: TAZORAC® Cream is not for oral use. Oral ingestion of the drug may lead to the same adverse effects as those associated with excessive oral intake of Vitamin A (hypervitaminosis A) or other retinoids. If oral ingestion occurs, the patient should be monitored and appropriate supportive measures should be administered as necessary.

OVERDOSAGE:  

- No specific therapy for TAZORAC® Cream overdosage. Treatment is symptomatic and supportive, with special attention to the patient's skin condition.

ADVERSE REACTIONS:  

- The most frequent adverse reactions reported during clinical trials with TAZORAC® Cream 0.1% in the treatment of acne were drying, burning, stinging, redness, irritation, rash, and discomfort. These effects were more common in patients treated with 0.1% tazarotene cream.

Drug Interactions:  

- Tazarotene may increase the effects of anticoagulants, including warfarin. Monitor patients closely for changes in the prothrombin time or other coagulation tests.

Nursing Mothers:  

- Tazarotene is a teratogenic substance, and it is not known what level of exposure is required for teratogenicity in humans. Caution should be exercised when tazarotene is administered to nursing women.

Pediatric Use:  

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

Geriatric Use:  

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

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COLLEGE OF DERMATOLOGY

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OCTOBER 23 - 26, 2005
THE ORLANDO CONVENTION CENTER, ORLANDO, FLORIDA
R.S.V.P. BECKY MANSFIELD (800) 449 - 2623

OCTOBER 23-26, 2005
Dystrophic Calcinosis Cutis


*4th year medical student at Kansas City School of Medicine and Biosciences-Kansas City, MO
**Affiliate Associate Clinical Professor of KCOM Dermatology Dept, Texas division, Dermatology Institute of North Texas

ABSTRACT

Calcinosis Cutis is characterized by deposition of calcium salts in the subcutaneous tissues of the body. In this report, a case of dystrophic calcinosis cutis with previous history of thermal burn at the same site.

Introduction

Calcinosis cutis is uncommon calcifying disorder of the skin; it is divided into four major types according to the etiology: dystrophic, metastatic, iatrogenic, and idiopathic. Dystrophic calcinosis include condition in which calcification occur in the damaged tissues. Metastatic calcification is deposition of calcium in normal tissue when there is dysfunction of calcium regulatory systems. Hyperparathyroidism, destructive bone disease eg. Paget disease, milk-alkali syndrome, sacrooidosis, and chronic renal failure are examples of this form of calcification. Deposition of calcium most often occurs within visceral organs rather than the skin or muscle. Idiopathic calcinosis cutis, occur in the absence of known tissue injury or systemic metabolic defect with normal serum calcium. Examples are calcinosis universalis, scrotal calcinosis the most common, tumoral calcinosis and subepidermal calcified nodule which are common in early childhood. Iatrogenic calcinosis cutis, is associated with medical procedures or treatment. Intravenous administration of calcium chloride may cause precipitation of calcium salts leading to calcification. This also occurs after diagnostic procedures such as EMG and EEG. The electrode paste contain calcium on braded skin leading to calcification at the site of electrode insertion.

Case Description

A 74 year old white male presented with a chronic ulcer on the right knee that has been present for four months. Patient states that this ulcer has occurred in the past and healed with scarring. He gave a previous history of a thermal burn during childhood in the right knee and thigh. (Fig 1) Past medical history was significant for hypertension and gastroesophageal reflux disease of both legs which are controlled by hydrochlorothiazide/quinapril (Accuretic), metoprolol (Toprol), pravastatin (Pravochol), and esomeprazole (Nexium). No known drug allergies. Social history was unremarkable regarding alcohol and drugs.

Wound healed with secondary intention and granulation. Patient developed a white-yellow papular eruptions on the surface of the right knee and the right thigh that were very tender and painful with central hardness and erythema. The nodule measured 22 x 10mm with a whitish central hole measuring 2 mm. (Fig 2) Due to the increasing discomfort in this nodule, an excisional biopsy was performed on 4/28/04. Another excisional biopsy was done on the last appearing nodule on the right thigh on 2/08/05. The pathology report of the two biopsies revealed islands of basophilic calcium salts present in the dense sclerotic connective tissue in the dermis. These findings support the diagnosis of calcinosis cutis secondary to prior trauma, in our case it was the thermal burn of the right knee/ and leg. The patient’s lab reports were obtained from his primary care provider to observe his calcium level; on two occasions his calcium level was within normal limit and performed during the patients flare up of eruptions.
Discussion

Dystrophic calcinosis cutis occurs in the setting of normal serum calcium and phosphate levels. The primary abnormality is damaged, inflamed, neoplastic, or necrotic skin. Burns, acne lesions, insect bites and necrotic tissue produced by infections such as cryptococcosis all cause localized tissue damage that may lead to extraosseal calcification. Generalized tissue damage such as CREST (calcification, raynaud phenomena, esophageal dysfunction, sclerodactyly, telangiectasias) variant of scleroderma, systemic lupus and progressive systemic sclerosis predispose to calcification in the hands, upper extremities and over bony prominences which appear as firm, whitish dermal papules, plaques, nodules or subcutaneous nodules that may become spontaneously ulcerated and extrude a chalky white material. In dermatomyositis, 50-70% of children will develop calcification depositing in the elbows, knees, buttocks and shoulders sparing the digits. While in the adult dermatomyositis, 20% of patients develop calcification.1,5

Some cases in newborns, panniculitis tissue necrosis results in nodules and plaques that may become calcified. Other conditions of inherited disorders such as Ehlers-Danlos syndrome, Porphyria cutanea tarda, Werner syndrome, Rothmund–Thomson syndrome and Pseudoxanthoma elasticum may be accompanied by cutaneous calcification.

Generally, the extrusion of calcium through the skin cause extreme morbidity with pain and possible secondary infection. In its most severe form, calcinosis universalis, the calcium deposits along the facial planes leading to functional impairment. Therapy of calcifying disorders is difficult. Some suggested treatments include surgical removal in selected patients with localized masses that are painful or interfere with function but recurrence is common after excision. Other therapies have been tried for dystrophic calcinosis include magnesium and aluminum antacids, probenecid, colchicine, low calcium and phosphate diet, sodium etidronate and diphosphonates though none of these have been convincingly shown to lead to improvement. The use of diltiazem, a calcium channel blocker, over the last 6 years has been reported to decrease the size of calcium deposits through the antagonistic effect on the calcium-sodium ion pump.4

Calcinosis cutis is usually by itself a benign disease and that prognosis is determined by the underlying disorder.

References:
Physician Assistants in Dermatology: Understanding the Effects of the Sun on the Skin

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ABSTRACT

Healthy benefits from solar radiation are very few. The harmful effects from the sun are preventable with proper education and action. Adverse effects of the sun and ultraviolet (UV) radiation can be acute, such as sunburns or chronic, such as actinic keratoses, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Patients with skin types I and II are at highest risk for sunburn and skin cancer. Preventative treatment, including the proper use of sunscreen beginning at a young age, self-skin examinations and periodic skin examinations by medical healthcare professionals who are trained in evaluating skin disease, is the optimal way to reduce potentially serious skin pathology that solar radiation may cause.

Introduction

Excessive sunlight can cause multiple problems to the skin. Patients are exposed to the most amount of sun in the first 20 years of their lives. Therefore, the greatest sun damage occurs during this time period. Learning safe habits early in life is easier than changing old habits later. Safe habits can help prevent sun damage in the future. For this reason, it is very important for healthcare professionals and parents to understand the risks of excessive sun exposure and how to protect children from the adverse effects of the sun. At least 90 percent of skin cancers are solar related, many of which can be prevented with increased awareness.

The harmful effects of solar radiation on skin, include acute and chronic changes. Preventative measures that should be taken to avoid these complications will be discussed. Proper clothing and sunscreen are necessary to protect against UVA and UVB radiation. Without proper protection, patients are at risk for sunburns and the adverse sequelae. Adverse effects from chronic sun exposure include actinic keratoses, basal cell carcinoma, squamous cell carcinoma and possibly an increase in malignant melanoma.

Recent studies have shown less of an association between sun exposure and malignant melanoma, and a greater association between a positive family history and malignant melanoma. Risk factors that increase a patient’s likelihood of developing these complications include: proximity to the equator, altitude, fair skin color, occupation and the time of day and time of year when the patient is exposed to the ultraviolet radiation. Many skin changes that were believed to be due to normal aging, such as easy bruising and wrinkling, are actually the result of prolonged sun exposure.

Most healthcare professionals are aware of the adverse effect of chronic sun exposure. It remains imperative that they include ‘sun awareness’ in each patient encounter.

Methods

The information in this manuscript was obtained from various online databases, journals and books. The databases include Up to Date, Medline Ovid, and Medline PubMed. Journal articles were obtained from Cutis and The Journal of the American Osteopathic College of Dermatology. The articles for used for this paper were all published after Jan 1, 2003. The referenced medical textbooks were found at the medical library at Nova Southeastern University.

The keywords that were searched include: sunscreen, sun protection, sunburns, ultraviolet radiation, actinic keratoses, basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Any article that was not written in English was excluded.

The skin remains the largest organ of the body. It consists of three main layers: epidermis, dermis, and sub-dermis. The epidermis is the thin tough, outer layer of the skin, which does not contain any blood vessels. The outermost layer of the epidermis, which is composed of mainly dead cells, is called the stratum corneum. This layer is somewhat waterproof and helps protect foreign substances from entering the body. The dead flat cells on the surface of the epidermis contain keratin, which is a tough and fibrous protein. Keratin forms the basic structure of the skin, hair and nails. The cells of the stratum corneum are shed and replaced every fourteen to twenty-eight days.

The dermis, which is below the epidermis, is composed of collagen and fibrillin. This layer allows for the skin’s flexibility and strength. This layer contains nerve endings, sweat glands, sebaceous glands, hair follicles, and blood vessels. In the deep dermis, there are melanocytes. These melanocytes produce melanin, which is the pigmentation of the skin. Melanin’s function is to filter out ultraviolet radiation (UV) from sunlight and provide color to the skin. The skin’s color is partially determined by the amount of melanin that the melanocytes produce and distribute to the overlying cells. The amount of melanin that is produced is dependent on hereditary factors and on the amount of time the skin is exposed to UV radiation.(1)

The sub-dermis, which is located below the dermis, is the subcutaneous layer composed of fat and loose connective tissue. This layer helps insulate the body from heat loss, provides a cushioning protective layer and serves as a potential energy storage area.(1)

Ultraviolet Radiation (UV)

Ultraviolet radiation, invisible to the human eye, causes extreme harm to the skin. In small amounts, UV radiation can be beneficial by helping the body produce vitamin D. Chronic exposure to UV is the most important risk factor for the development of squamous and basal cell carcinoma. Sunlight can be broken down into bands of light according to its physical characteristics (wavelengths) and biological effects.

There are three types of UV radiation: UVA, UVB, and UVC. UVC, which has a wavelength between 100-290 nm, is filtered by the atmospheric ozone and little is able to reach the earth’s surface. UVB radiation has a wavelength between 290 – 320 nm. This radiation is known as “midrange” radiation and it is not completely filtered by the atmospheric ozone. UVB radiation is responsible for sunburns. UBV injures skin
cells through the formation of DNA thymine dimmers and DNA 6-4 photoproducts. Gene mutations leading to carcinogenesis can result if these injuries are not properly repaired.(2)

UVA radiation has a wavelength between 320 – 400 nm. UVA is not filtered by the earth’s atmospheric ozone layer, resulting in a 150-fold greater amount of UVA reaching the earth’s surface than UVB. UVA can penetrate deep to the basal layer and capillary bed of exposed skin, playing a major role in photo-aging. It is believed to interfere with the cutaneous immune system. It can directly damage the antigen presenting cell, which may cause the release of immunosuppressive cytokines, such as interleukin 10 and tumor necrosis factor (TNF), causing the isomerization of trans-urocanic acid to cis-urocanic acid. This contributes to the formation of a reactive oxygen species, causing oxidative damage to DNA. This immunologic effect can increase the risk for skin cancer.\(^2\)

UV radiation is strongest between the hours of 10 am and 3 pm. UV radiation is more intense during the summer months and at higher altitudes. Some researchers believe that the amount of UV radiation reaching the earth is greater now than in the past due to the depletion of the ozone layer.\(^6\)

Ultraviolet radiation is the major contributor to skin damage. Ultraviolet rays injure the skin’s cells in the epidermis and then penetrate into the deeper layers of the skin. The initial effect from UV radiation is sunburn. The long term adverse effects of continued exposure to UVA and UVB can lead to skin cancer and premature aging of the skin.

**Sun Protection**

The proper use of sunscreens can help prevent the sun’s harmful effect on the skin. The use of sunscreen beginning at a young age can help prevent a patient from having a future consisting of wrinkles, dyspigmentation and skin cancer. Optimal sun protection includes using sunscreen, wearing a hat, sunglasses, long-sleeved shirts and long pants.

Sunscreens that can help prevent basal cell and squamous cell skin cancer must prevent UV radiation immunomodulation. A sunscreen’s effectiveness is based on how well it is able to prevent erythema. Sunscreens are given a sun protective factor (SPF) number. The higher the number, the greater degree of protection. A SPF 15 has a 93 percent protection rating. A SPF 30 has a 96 percent protection rating, while a SPF 60 has a 98 percent protection rating. The duration of effectiveness can be determined by multiplying the SPF by the length of time it takes for erythema to occur without sunscreen. For example, if it normally takes a patient 10 minutes to develop erythema while exposed to the sun, then by using a sunscreen with a SPF of 15, it should take the same patient about 150 minutes to develop an equivalent degree of erythema.\(^8\)

Sunscreen should be applied daily and frequently. Sunscreen helps to block the UV radiation absorption by the skin. When deciding on the right sunscreen, the most important item to look for is a SPF of 15 to 30, or greater. Since UVA appears to contain the wavelength that leads to skin cancers, the sunscreen selected should contain ingredients that selectively block out as much UVA as possible. If the patient experiences excessive sweating or goes swimming, the sunscreen must be reapplied more often. Children older than 9 months should use sunscreen daily.\(^8\) If the patient participates in activities with excessive sun exposure, then clothing, such as Solumbra\(^x\) or FrogWear\(^x\) are helpful.

Most patients do not apply enough sunscreen on their bodies. In order to cover the whole adult body, approximately 1 oz. of sunscreen is needed, which is about a handful. Sunscreen should be applied 30 minutes prior to sun exposure, and then reapplied every 2 hours.

Sunscreen has not been proven to prevent malignant melanoma. One recent study showed no association between developing melanoma and the use of sunscreen. Many patients believe that they are protected from developing melanoma by using a sunscreen.\(^9\) Sunscreen is extremely important for the role that it plays in preventing sunburn and photo-aging, actinic keratosis, squamous cell and basal cell carcinoma and possibly reducing the incidence of malignant melanoma.

**Sunburns**

Without the proper use of sunscreen, patients are exposing themselves to an increased risk of acquiring sunburns. Sunburns can range from a mild to a severe and painful burn. The most severe reactions come from prolonged exposure such as when a patient falls asleep in the sun. The intensity of the burn depends on the length and intensity of exposure, the patient’s complexion, and the previous condition of the patient’s skin.

How a patient’s skin will react to sun exposure can be categorized by “skin typing.” Dr. Fitzpatrick described six different skin types. Type I skin always burns and never tans. Type II skin usually burns and tans with difficulty. Type III skin usually tans, but can get a non-tender sunburn. Type IV rarely burns and tans with ease. Type V skin is brown, tans easily and does not burn. Type VI skin is black in color and does not burn.\(^9\)

Certain medications may increase a patient’s sensitivity to sunlight. This photodrug reaction can range from erythema or a measles-like rash to a severe bullous eruption. This reaction usually develops between two and twelve hours after the sun exposure. Vesiculation may be associated with a photo-drug reaction. Systemic weakness, malaise, chills and possible local pain may be associated with a photodrug reaction. Scaling and/or peeling can occur three or four days after the primary reaction.\(^*\)

Prophylactic treatment is the best way to prevent sunburns. This includes the proper use of sunscreen as well as a sensible and gradual exposure to the sun. If a patient does present with a sunburn, the proper treatment may include the use of aspirin to reduce the inflammation, application of cool and wet compresses for 20 minutes five times a day, increase fluid intake, topical corticosteroids and avoidance of sun exposure until skin is completely healed.

**Skin Cancer and Actinic Keratosis**

Skin cancer is the most common malignancy. The three most common types of skin cancers include basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma. Actinic keratoses (AK’s) are considered by most dermatologists to be pre-malignant lesions that have can transform to SCC’s.

Actinic keratoses develop only on sun-damaged skin. AK’s may represent a clone of abnormal squamous cells induced by UV radiation. SCC may then develop from an AK after further gene alteration. Most AK’s will not progress to an SCC. The rate of transformation of AK to SCC during a patient’s lifetime is controversial. The range of transformation has been reported anywhere from 0.2 to 8 percent in the medical literature. However, 60% of SCC’s originated as an AK.\(^8\)

AK’s presents as an erythematos hyperkeratotic macule. They appear most often on the neck, forearms, hands and upper back. Less commonly, they can appear on the pre-tibial area. The differential diagnosis of an AK includes: seborrheic keratoses, verruca vulgaris, SCC and BCC. The erythematous base of an AK can help to distinguish it from a seborrheic keratosis. The hyperkeratosis of an AK is usually hard or spine-like and irregular, whereas the hyperkeratosis of seborrheic keratosis is usually smooth and usually soft.\(^x\)

Prevention is most important when discussing AK’s. Avoiding sun exposure and the proper use of sunscreen will dramatically decrease the risk of developing AK’s. Once an AK has developed, the proper

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because of their low metastatic potential, however, they are potentially locally invasive and destructive.\(^{(10)}\)

The risk of developing a BCC increases with age. Patients between the age of 55 and 75, are 100 times more likely to develop a BCC than patients under the age of 20. In the United States, the incidence of developing a BCC in a patient’s lifetime is between 5-10 percent. Men are 30 percent more likely to develop a BCC. BCC’s are uncommon in dark-skinned populations. Patients in the United States that live closer to the equator, such as Hawaii, Florida and California, experience a greater incidence of BCC. Australia has the highest incidence of BCC.\(^{(12)}\) Populations that live at higher elevations, also experience a greater incidence of BCC.

The risk factors for developing a BCC include environmental and genetic factors. People with fair skin, light-colored eyes, red hair, northern European ancestry, older age, childhood freckling, and an increased number of past sunburns, have a greater chance of developing a BCC. Childhood sun exposure seems to be more critical then adult sun exposure in the development BCC’s. Aggressive sun protection before the age of 18 can reduce the risk of non-melanoma skin cancer by 78 percent. It has been shown that intermittent, intense sun exposure increases the risk of BCC more than a similar dose delivered continuously over the same period of time.

Basal cell carcinomas typically appear in sun-exposed areas. Seventy percent occur on the face, of which 25 – 30 percent occur on the nose. Only 15 percent occur on the trunk. Infrequently, BCC may appear on the penis, vulva, or perianal area.\(^{(13)}\)

BCC’s typically present in one of three forms: nodular, superficial, and morpheaform. Nodular BCC is the most common type of BCC, comprising 60% of all BCC’s. Nodular BCC usually presents on the face as a pink or flesh colored papule, with a pearly and translucent quality. A telangiectatic vessel is usually visible within the papule. These tumors are known as the “rodent ulcer” because ulceration is commonly seen. The differential diagnosis for nodular BCC can include: benign growths such as dermal nevi, small epidermal inclusion cyst, sebaceous hyperplasia, and molluscum contagiosum.\(^{(16)}\)

Superficial BCC’s are the second most common type of BCC, averaging around 30% of all cases of BCC. These tumors tend to appear on the trunk. Superficial BCC’s generally appear as a pearly papule or plaque that is a light red color. These tumors may be atrophic in the center and usually have a fine translucent papular rim. Superficial BCC is more common in men than in women. The differential diagnosis for superficial BCC include: SCC, keratoacanthomas, metastatic disease from inter-}

**Basal Cell Carcinoma**

Basal cell carcinoma (BCC) is the most common type of skin cancer and constitutes 75 – 80 percent of all non-melanoma skin cancers. The name is derived from the origin of the tumor, which is in the basal layer of the epidermis. These tumors are sometimes referred to as epitheliamas
developing a second BCC within 3 years. A patient with a history of a BCC is also at an increased risk of developing a SCC or malignant melanoma. For this reason, it is important for these patients to have full body skin checks every 6-12 months by a healthcare professional that is familiar with skin evaluation.

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common non-melanoma skin cancer. SCC’s compromise 20 to 25% of all non-melanoma skin cancers. Over 60% of SCC’s develop from an AK. SCC received its name because the lesions are squamous intraepithelial lesions. SCC’s are more aggressive than BCC’s and are more likely to metastasize. SCC’s developing from AK’s have 0.5% likelihood to metastasize. SCC arising on the lower lip has a 16% incidence of metastasis. SCC’s arising in the areas of burn, scars, draining sinuses, and modified epithelium are also more likely to metastasize.

SCC is most commonly found in Americans over the age of 55. In Australia and New Zealand, SCC is commonly found in patients in their 20’s and 30’s. The incidence of SCC is increased in fair-skinned patients who have had excessive sun exposure.

SCC occurs most commonly on skin that is chronically exposed to the sun. These areas include the face, scalp, dorsal hands, dorsal arms, the “V” of the neck, the back of the neck and the chest. SCC’s may resemble BCC’s, AK’s or warts in appearance. They are often ill-defined, erythematous macules with a rough surface. Typically, a SCC increases in elevation and depth as they grow. SCC’s are more likely to have an overlying scaly surface than BCC’s. Three common variants of SCC include verrucous carcinoma, keratoacanthomas and superficial Bowen’s disease.

The scaly surface may project from the skin and form a cutaneous horn as seen in verrucous carcinoma. Similar to warts, these tumors usually develop on the hands and the feet, but can also arise in the anogenital area and on the oral mucosa.

Keratoacanthomas (KA’s) are rapidly growing hyperkeratotic nodules with a central keratin plug. These tumors appear suddenly as skin colored papules or nodules. They are faster growing than other SCC’s, usually reaching a size of 1-2 cm’s. If left untreated, KA’s usually spontaneously regress. Approximately 10 percent of all KA’s will develop into an invasive SCC. KA’s almost always appear in sun-exposed areas.

Bowen’s disease is a form of SCC in situ. Bowen’s tumors may appear on any area of the skin. Bowen’s disease presents as a persistent, erythematous, slightly indurated macule or patch with a variable amount of scaling. The differential diagnosis for Bowen’s disease includes: Paget’s disease, extramammary Paget’s disease and superficial spreading BCC. A pigmented Bowen’s tumor may resemble a malignant melanoma.

Surgical excision is the treatment of choice for SCC’s. Cure rates with simple excision are greater than 90 percent. The cure rate reaches 97 percent with Moh’s micrographic surgery. Radiation therapy treatment for SCC has a lower cure rate than for BCC, but is can be used in cases where surgery is contraindicated. For small non-aggressive, in-situ SCC’s, treatment may include: curettage with electro-destruction, cryosurgery, or excision. For larger and aggressive SCC’s, treatment may include: excision with frozen section for microscopic margin evaluation, Moh’s micrographic surgery or radiation therapy. If lymphatic spread of the tumor is suspected, then a lymph node dissection may be indicated. KA’s may be treated with a deep shave plus curettage, curettage with electrodessication, intralesional 5-fluorouracil, cryosurgery, or excision. Bowen’s disease may be treated with curettage and electro-destruction, topical fluorouracil, imiquimod, cryosurgery, laser, or excision. In order to help prevent SCC’s from developing, the proper use of sunscreen starting at a young age is necessary.

The prognosis for SCC depends on the size and location of the tumor, histological pattern, depth of invasion, perineural involvement and immunosuppression of the patient. The overall metastatic rate for a SCC on the ear is 11 percent, on the lips is 14 percent, and an overall rate from all sites is 5 percent. Lesions less than 2 cm have a recurrence rate of 7 percent after excision. Lesions greater than 2 cm have a recurrence rate of 15 percent.

Malignant Melanoma

Malignant melanoma is the sixth most common cancer in the United States. It is the most common cancer in patients between the ages of 25-29. The lifetime risk of developing a melanoma is increasing. It is estimated that 1 in 100 patients born in 1990 will develop a melanoma and that this will increase to 1 in 75 patients born in the year 2000. Approximately 7900 deaths per year in the United States are attributable to malignant melanoma. The overall survival rate from melanoma has increased from 50 percent in the year 1975 to 90 percent in the year 1999. This is mainly due to patient and health provider awareness of melanoma, which has led to earlier diagnosis and therefore a less ominous tumor.

The risk factors for developing a melanoma include patients with fair complexion (skin types I and II) and those patients who are in the sun for short, intensive periods of time. Individuals with multiple atypical appearing melanocytic nevi or large congenital melanocytic nevi are also at an increased risk for developing a melanoma. Patients with a history of melanomas or family history of melanoma are also at an increased risk. Approximately 10 percent of melanomas have a familial pattern. A patient with a first degree relative with a history of a melanoma has an 8 to 12 fold increase in the risk of developing a melanoma.

There are many clinical presentations for melanoma. They usually began as a solitary lesion. Only about 20 percent of malignant melanomas arise from pre-existing melanocytic nevi. When malignant melanoma develops from preexisting nevi, the nevi begin to change in appearance, and new ones begin to bleed. Early melanomas are characterized by having different colors, such as red, black, brown and blue. Melanomas may also present as a brown or black discoloration of the nail or as a skin ulcer that does not heal. Melanomas may arise on any part of the body independent of sun-exposure. In women the most common location for a melanoma is on the lower extremities. In men, the most common location is on the trunk.

There are five different types of melanomas, including superficial spreading, nodular, acral lentigious, lentigo maligna melanoma and amelanotic melanoma. Superficial spreading melanomas are the most common type of melanoma, comprising 70% of all melanomas. They appear as a slow growing brown or black spot that can have either a macular or papular component. The lesion usually shows color variation or irregular borders.

Nodular melanomas comprise 15 to 30 percent of melanomas. They appear as a brown or black pigmented papule that slowly enlarges and frequently ulcerates.

Acral lentigious melanomas comprise about 5% of all melanomas, however it is the most common melanoma in persons of color. It usually appears as a brown or black macule arising on the non-hair baring areas of an extremity, such as the palms, soles and nail beds.

Lentigo maligna melanoma comprises about 5% of all melanomas. It usually presents as an irregularly shaped, flat, pigmented lesion on sun damaged skin. It occurs most often on the face or other chronic sun exposed areas. Advanced lesions can develop into papules or nodules, indicative of vertical or downward growth.

Amelanotic melanoma is a non-pigment producing variant of a nodular melanoma. It is commonly confused with BCC’s or benign skin lesions.
The ABCD’s of a melanoma are helpful for determining which lesions are suspicious for melanoma. A is for asymmetry. This includes any nevus which appears asymmetric in shape or in pigment distribution. B is for border and bleeding. Any nevus with irregular or ill-defined borders should make one suspicious. Any bleeding mole also requires careful evaluation. C is for color. Any mole that has a pigment variation in an otherwise homogeneous nevus must be carefully evaluated. D is for diameter. Most melanomas are greater than 6 mm in diameter, however it is possible for melanomas to be smaller than 6 mm.10

In order to stage malignant melanoma, two systems were developed. Clark’s level and Breslow’s depth. Clark’s level classifies the tumor based on the degree of invasion into different anatomical levels of the skin. In level I, the tumor is confined to the epidermis. In level II, the tumor cells extend into the papillary dermis. In level III, the tumor cells fill the papillary dermis. In level IV, the tumor cells extend into the reticular dermis. In level V, the tumor cells extend through the reticular dermis and into the underlying subcutaneous fat.

Clarks level I has nearly a 100 percent five-year survival rate. Patients with Clark’s level II have a greater than 95 percent five-year survival rate. Patients with a Clark’s level III have greater than 90 percent five-year survival rate. Patients with a Clark’s level IV have only a 75 percent five-year survival rate. Patients with a Clark’s level V, have less than a 50 percent five-year survival rate.

Breslow’s depth is a more precise assessment of the level of invasion of a malignant melanoma. An ocular micrometer is used to measure the distance from the granular layer of the epidermis to the point of the deepest invasion by the tumor cells. A depth of .75 mm or less has a 99 percent five-year survival rate. A depth of 1.50 – 4.00 mm has a seventy-five percent five-year survival rate. A depth greater that 4.0 mm is only a 42 percent five-year survival rate.

Excision is the treatment of choice for a melanoma. A wide local excision of the primary tumor to the muscle fascia is recommended. For melanomas in situ, a margin of 0.5 cm is recommended. A 1 cm margin is recommended for melanomas less than 2 mm thick. A 2 cm margin is recommended for melanomas greater than 2 mm thick. Lymph node dissection is indicated for patients with evidence of lymph node involvement in discrete drainage basins. A sentinel lymph node biopsy may help to identify which patients will benefit from elective lymph node dissection therapy.11

Patients with a history of melanoma, or that have a first-degree relative with a history of melanoma, must have follow-up skin examinations for the rest of their lives. The examination should be directed toward the detection of any local recurrence of the primary tumor and the development of metastatic disease in the surrounding skin. Examination of the lymphatic system is equally important. The examiner should also look for the signs of a secondary melanoma or distant metastasis. Early detection of a melanoma can be life saving. Skin self-examinations are of value for early detection in patients that are at an increased risk for developing melanomas.12

Patient Education

Healthcare professionals should include education on sun protection to all patients, especially parents and their children. Patients should be advised to stay out of the sun from 10 AM to 3 PM., which are the peak hours of UV radiation. Patients should be advised to wear sun protective clothing, such as wide brimmed hats that protect their face and neck, tightly woven clothing, dark clothing with dyes that absorb UV radiation, long sleeved clothing, and clothing with an SPF factor. Patients should also be advised on the importance of wearing sunscreen with a SPF factor of 15 or greater during daylight hours. Sunscreen should be reapplied every 2 hours. Patients should be instructed to examine their skin monthly and to bring any suspicious changes in their moles to the attention of a healthcare professional trained in the diagnosis and treatment of diseases of the skin. A basic overview of the ABCD’s of pigmented skin lesions should be discussed with all patients, to assure that they are able to recognize suspicious changes in their moles. Patients should also be advised to have their skin checked by a healthcare professional on a yearly basis.

Conclusion

The sun can have harmful yet preventable effects on the skin. In order to reduce the harmful effects, patient education is imperative. Patients should be made aware that sun damage is cumulative and that each exposure to the sun increases their risk of these harmful effects. The majority of sun damage occurs during the patient’s first 20 years of life. Patients must institute proper protective measures at a young age and become ‘sun smart’. Prevention begins with education, proper sunscreen use, proper clothing attire, and avoiding sun exposure during peak UV hours. The importance of sunscreen is its ability to block UV radiation, which can cause photo-aging and skin cancers. UVA and UVB are both carcinogenic and responsible for over 90 percent of all skin cancers. With prolonged solar exposure, patients are increasing their risk of developing actinic keratoses, basal cell carcinoma, squamous cell carcinoma and possibly malignant melanoma. Patients with Fitzpatrick skin types I and II are at an increased risk for developing skin cancers. One in 7 Americans will develop a skin cancer during their lifetime. Recent studies show less of a relationship between sun exposure and melanomas and a greater association between a positive family history and developing a melanoma. As more clinical studies are performed, the importance of educating patients about the harmful effects of sun exposure becomes more clear. With education, prevention and early and proper diagnosis, we can help improve the health of our patients.

References:

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