Chicago Dermatological Society

December 2008
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, December 10, 2008

Conference Host:
Department of Dermatology
University of Illinois at Chicago
Chicago, Illinois

Chicago Dermatological Society

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CDS Monthly Conference Program
December 2008 -- University of Illinois at Chicago

December 10, 2008

8:30 a.m.	**REGISTRATION, EXHIBITORS & CONTINENTAL BREAKFAST** *Student Center West*
9:00 a.m. - 10:00 a.m.	**RESIDENT LECTURE** Multidisciplinary Cutaneous Oncology Clinic *KEVIN D. COOPER, MD*
9:30 a.m. - 11:00 a.m.	**CLINICAL ROUNDS** Patient & Slide Viewing *Dermatology Clinic*
11:00 a.m. - 12:00 p.m.	**GENERAL SESSION** *Student Center West*
11:00 a.m.	CDS Business Meeting
11:15 a.m.	Psoriasis: Treatments as a Window to New Concepts in Immunopathogenesis *KEVIN D. COOPER, MD*
12:15 p.m. - 1:00 p.m.	**LUNCHEON**
1:00 p.m. - 2:30 p.m.	**AFTERNOON GENERAL SESSION** Discussion of cases observed during morning clinical rounds *WARREN PIETTE, MD, MODERATOR*

CME Information

This activity is jointly sponsored by the Chicago Medical Society and the Chicago Dermatological Society.

This activity has been planned and implemented in accordance with the Essentials Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the Chicago Medical Society and the Chicago Dermatological Society. The Chicago Medical Society is accredited by the ACCME to provide continuing medical education for physicians. The Chicago Medical Society designates this educational activity for a maximum of four (4) *AMA PRA category 1 credits*™. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Commercial Support: There are no educational grants associated with this meeting. One or more companies may pay a fee to be present as exhibitors. The program content is free from any commercial or corporate influence.

Guest Speaker

Kevin D. Cooper, MD
Professor & Chair, Department of Dermatology
Case Western Reserve University, Cleveland, OH

In addition to serving as chairman of the Department of Dermatology at Case Western Reserve University, Dr. Cooper also is director of the University's NIAMS Skin Diseases Research Center and also the Murdough Family Center for Psoriasis at the university hospitals. He is a graduate of the University of Florida College of Medicine (1977) and completed his dermatology residency at the Oregon Health Sciences University in Portland (1981). He also completed fellowships at the NIH National Cancer Institute. Dr. Cooper is board certified in Dermatology, Dermatologic Immunology/Diagnostic & Laboratory Immunology.

Speaker CME Disclosure of Financial Interests

Dr. Cooper has disclosed the following financial relationships: Consultant - Genmab, Estee Lauder, L'Oreal, Daiichi Asubio, Vindico, Boehringer Ingleheim, PanGenetics, Proctor and Gamble, Astellas, Avera Pharmaceuticals, ZymoGenetics Inc.; Speaker - Rockefeller University; Cornell University; Proctor and Gamble; Investments - Medarex, AGI Dermatics; Royalties - University of Michigan patent (Alefacept).

CME Credit Documentation

Following the meeting, the Chicago Medical Society will send you a certificate documenting your attendance at this conference and the number of Category 1 CME credits you earned. It is essential that you sign the CME attendance sheet at the CDS registration desk before you leave the conference. If you have any questions about your credits, please contact the Chicago Dermatological Society by phone: 847/680-1666; or by email: RichardPaul@DLS.net

Evaluation Forms

Please complete and return your meeting evaluation form. This feedback is an important part of the CME process and helps us to design programs in the future that better meet the needs of our members. Note that the form will be scanned by computer; keep your responses within the spaces provided, and avoid making any extraneous marks on the sheet. Thank you!

University of Illinois at Chicago
Department of Dermatology

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Acknowledgements: *Eric Aaltonen, MD, Seema Pasha Apichai, MD, Deborah Giusto, MD and Kim Yancey, MD*

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Case Presented by Deborah Marble, MD
and Iris Aronson, MD

History of Present Illness:
This 69 year old female was originally referred for management of hidradenitis suppurativa of the buttocks and perineum. The patient presented with a history of draining nodules and sinuses of the buttock since 2006, which began shortly after hospitalization for surgical excision of a large cell neuroendocrine carcinoma of the lung. The patient denied any previous history of similar lesions on the buttock, inguinal folds, axillae or other parts of the body. Shortly after presentation, the patient developed an ulcer on her left lower leg which started as a small pimple and quickly ulcerated.

Past Medical and Surgical History:
Large cell neuroendocrine carcinoma of the lung status post left upper lobectomy (negative lymph nodes and surgical margin), diabetes, deep vein thrombosis, degenerative joint disease, total abdominal hysterectomy and oophorectomy for endometriosis, bunionectomy

Medications:
Miconazole 2% ointment, fluconazole, folic acid, ferrous sulfate, levofloxacin, lidocaine 2% topical jelly, amoxicillin-clavulanate, amoxicillin, morphine, insulin glargine, glipizide, furosemide, and tramadol

Allergies:
Propoxyphene and iodinated radiocontrast dyes

Family History:
No history of hidradenitis suppurativa

Social History:
The patient is a retired nurse with no history of tobacco or ethanol use.

Review of systems:
Occasional joint pain and myalgias; no nausea, vomiting, fever, chills, cough, or weight loss

Physical Examination:
Within the gluteal cleft and medial buttocks, extending onto the perineum and labia majora, are large confluent erythematous and edematous plaques of deep and superficial nodules with occasional sinus tracts. There is drainage of malodorous yellowish fluid. On the left anterior tibial region is a 7cm x 4cm erythematous irregular thin ulcer with yellow exudate. Axillae are clear.

Laboratory Data:
The following were positive or abnormal:
Alkaline phosphatase 190u/l (40-125), albumin 1.9g/dl (3.4-5), iron 33ug (37-140), hemoglobin 9.7g/dl (11.7-16), hematocrit 30% (35-49), mean corpuscular volume 76.1fl (80-99), and erythrocyte sedimentation rate 93mm/hr (0-20).

The following were negative or within normal limits:
White blood cell count, platelets, electrolytes, liver function tests excluding alkaline phosphatase, magnesium, phosphorus, total iron binding capacity, anti nuclear antibody, total hemolytic complement (CH50), factor V Leiden, protein C, protein S, and anticardiolipin antibodies.

Diagnostic Procedures and Tests:
05/08 Tissue culture, buttocks: Moderate growth of *Actinomyces* species and *Bacteroides caccae*

06/08 Magnetic resonance imaging with and without contrast, pelvis: Extensive subcutaneous perineal sinus tract with surrounding soft tissue inflammation/cellulitis; no evidence of involvement of the deep pelvic structures or bones. There is pelvic lymphadenopathy. There is trace free fluid in the pelvis.

Histopathology:

05/08 Buttock: Biopsy shows ulcerated skin with deep dermal mixed inflammatory cell infiltrate including neutrophils, eosinophils, plasma cells, and lymphocytes. There is also marked dermal edema and pseudoepitheliomatous hyperplasia of the overlying epidermis. The PAS, GMS, and Gram stains are all negative. Correlation with culture result is necessary to completely exclude the infectious etiology.

06/08 Right leg: There is subcorneal pustulosis with a mixed infiltrate of neutrophils, eosinophils and lymphocytes in the superficial dermis.

Diagnosis:

Actinomycosis of the buttock and perineum

Treatment and Course:

Additional biopsies were not diagnostic for hidradenitis suppurativa and tissue culture of the buttocks grew *Actinomyces species* and *Bacteroides caccae*. The patient was referred to infectious disease for treatment of her infection. The patient subsequently developed an ulcer on the right ankle and increased ulceration of the left lower extremity. Although the ulcers were thought to be from polymicrobial infection, the right lesion grew *Candida parapsilosis* and the left grew *Pseudomonas*. The patient is presently being treated with fluconazole 100mg daily, levofloxacin 750mg every other day, amoxicillin-clavulanate 875mg twice daily, and amoxicillin 250mg twice daily.

Discussion:

Primary cutaneous actinomycosis is a rare suppurative, granulomatous infection, which is usually associated with trauma or ischemia. Most commonly actinomycosis presents as cervicofacial actinomycosis or "lumpy jaw," but it can follow an indolent course and have a variable presentation. Case reports from France describe actinomycosis of the perianal area and buttocks presenting as localized erythematous and violaceous nodules with fistulas. Most described cases were present for many months at the time of diagnosis. Hypothesized sources include endogenous cryptoglandular and appendix origin. There are reports of *Actinomyces meyeri* presenting with multiple skin abscesses following lung abscess with subsequent hematologic spread. Importantly, cutaneous actinomycosis is curable with surgical debridement and long courses of antibiotics.

Essential Lesson:

- Actinomycosis can mimic hidradenitis suppurativa on clinical exam.

References:

1. Apotheloz C. et al. Disseminated infection due to Actinomyces meyeri: case report and review. *Clinical Infection Disease* 1996; 22:621-625.
2. Bauer P et al. Perianal actinomycosis:diagnostic and management considerations: a review of six cases. *Gastroenterol Clin Biol* 2006; 30:29-32.
3. Gayraud A et al. [Cutaneous actinomycosis in the perianal area and buttocks]. *Ann Dermatol Venereol* 2000; 127:393-6.
4. Lerner P. The Lumpy jaw. Cervicofacial actinomycosis. *Infect Dis Clin North Am* 1988; 2:203-220.
5. Maradeix S. [Actinomycosis of the buttock]. *Ann Dermatol Venereol* 2005; 132:462-5.
6. Metgud S. Primary cutaneous actinomycosis: a rare soft tissue infection. *Indian J Med Microbiol* 2008; 26(2):184-6.

Case # 2

Case Presented by Sabrina Guillen Fabi, MD, Ronald Berne, MD and Iris Aronson, MD

History of Present Illness:
This 32 year old Mexican female presented with an 11 year history of chronic swelling, desquamation, and a burning sensation of her lower lip and partial upper lip. Prior to presenting to our clinic she was followed at an outside institution where she was diagnosed with "photosensitive lip dermatitis." The patient was prescribed various unspecified topical preparations that provided minimal relief. Two months prior to presenting to our clinic her condition worsened and a biopsy of her lower lip was inconclusive. She was subsequently started on triamcinolone 0.1% cream, mupirocin ointment, and an over the counter emollient which provided temporary relief. The patient denies any other affected areas. She also denies ever using makeup. She does admit that sunlight makes her rash worse.

Past Medical and Surgical History:
Pterygia bilaterally with conjunctival biopsies in 1995 and 2000 showing reactive lymphoid hyperplasia

Medications:
Loteprednol etabonate 0.5% ophthalmic suspension and an over the counter emollient

Allergies:
Amoxicillin – she develops swelling and erythema of her hands

Family History:
No history of skin cancer, skin conditions, autoimmune conditions, or pterygia

Social History:
The patient immigrated from Mexico at the age of 2. She is a stay at home mom and denies smoking.

Review of systems:
Denies fevers, weight loss, shortness of breath, chest pain, arthralgias, hematuria, or fatigue.

Physical Examination:
Conjunctival injection is present bilaterally. A yellow membrane forming over the inner corner of the left eye and outer corner of the right eye extends over the sclera to partially involve the cornea bilaterally. There is a hyperkeratotic, crusted plaque over the entire inferior lip and partially over the superior lip. An erythematous nodule with overlying serosanguineous crust is present on the tip of the nose.

Laboratory Data/Diagnostic Procedures and Tests:
The following were positive or abnormal:
Antinuclear antibody test 119 U/ml (negative<100, equivocal 100-120, positive >120), erythrocyte sedimentation rate 25mm/hr (0-20), and nasal biopsy tissue culture grew moderate *Staphylococcus aureus*

The following were negative or within normal limits:
Complete blood count with differential, complete metabolic panel, total hemolytic complement, C3, C4, and urine analysis. Tissue cultures of nasal biopsy for anaerobes, acid fast bacilli, and fungi.

Histopathology:
11/07 Lower lip: There is prominent lymphoid hyperplasia with germinal center formation. This is accompanied by a mixed dermal infiltrate of lymphocytes and eosinophils. There is no evidence of vasculitis. The overlying epidermis displays mild epidermal hyperplasia with focal erosion.

11/08 Nose: Same features as above. The PAS stain shows a normal appearing basement membrane and no evidence of fungal elements. Immunostains of CD3 and CD20 highlight mixed populations of T-cells and B-cells with a ratio that is within normal range.

Diagnosis:
Actinic prurigo

Treatment and Course:
The patient was instructed to discontinue use of any topicals to her face and lips and to use baking soda as a substitute for toothpaste. Strict sun protection was advised and application of 16% zinc oxide paste to her lips was recommended. Impetigo of the nasal nodule was treated with doxycycline 100 mg twice daily for 3 weeks. Subsequently, hydroxychloroquine at a dose of 200 mg daily was initiated.

Discussion:
Actinic prurigo (AP) is a rare, idiopathic chronic photodermatosis commonly affecting Latin American Mestizo and Native American girls, although it can occur at any age. The pathogenesis has not been clearly elucidated, but studies have suggested that it is an immune-mediated condition.

The polymorphic clinical features of AP include erythematous papules, nodules, crusts, and lichenified plaques due to chronic scratching. Cutaneous manifestations can appear hours to days following exposure to both ultraviolet A and B light on sun-exposed skin, and can persist during the winter. 65% of patients have cheilitis and in 10% of patients the lips are the only site of involvement. Eye involvement in the form of pseudopterygium, limbitis, and conjunctivitis is present in up to 45% of cases.

Histologic examination shows hyperkeratosis, regular acanthosis, mild spongiosis, edema of the lamina propria, and a dense lymphohistiocytic infiltrate that can have a band-like distribution, or occasionally form follicles. The latter is more common in the mucosa, conjunctivae, and the lips. Vacuolization of the basal cell layer, stromal edema, and dilated capillaries in the dermis are also noted.

Several conditions need to be considered in the differential diagnosis, including atopic dermatitis with photosensitivity, chronic actinic dermatitis, polymorphous light eruption, hydroa vacciniforme, discoid lupus erythematosus, erythropoietic protoporphyria, and Jessner's lymphocytic infiltrate.

Sun protection is the cornerstone of treatment. Topical steroids, emollients, and oral antihistamines may relieve the pruritus associated with AP and acute exacerbations can be mitigated by a short course of oral corticosteroids. Unfortunately, antimalarials and immunosuppressants, such as methotrexate, have only proven partially effective. To date, thalidomide is the most effective treatment option. Fortunately, there is no associated increase in mortality with this disease. However, AP can have an adverse impact on the quality of life because of the restrictions on outdoor activity and the cosmetic appearance of the rash.

Essential Lessons:
- Involvement of the lips and eyes are specific for the diagnosis of actinic prurigo
- When considering photodermatoses in Latin American patients, a thorough history and review of systems, including eye symptoms, is invaluable in narrowing the differential diagnosis.

References:

1. Herrera-Geopfert R, Magana M. Follicular cheilitis. A distinctive histopathologic finding in actinic prurigo. *Am J Dermatopathol* 1995; 17(4):357-61.
2. Hojyo-Tomoka MT, Vega-Memije ME, Cortes-Franco R, et al. Diagnosis and treatment of actinic prurigo. *Dermatol Ther* 2003; 16(1):40-4.
3. Lestarini D, Khoo LS, Goh CL. The clinical features and management of actinic prurigo: a retrospective study. *Photodermatol Photoimmunol Photomed* 1999; 15(5):183-7.
4. Ross G, Foley P, Baker C. Actinic prurigo. *Photodermatol Photoimmunol Photomed* 2008; 24(5):272-5.

Case # 3

Case Presented by Amber Stevenson, MD
and Lawrence Chan, MD

History of Present Illness:
This 63 year old male presented for evaluation of pain in his left nipple. Eight months prior, he had noticed retraction of his left nipple, followed by overlying crust formation, intermittent bleeding, and associated pain. Upon presentation, the pain had improved but he still complained of exquisite tenderness with manipulation.

Past Medical History and Surgical History:
Depression and an open reduction and internal fixation of the left knee with a skin graft after a motorcycle accident

Medications:
Bupropion

Allergies:
No known drug allergies

Family History:
Mother with breast cancer diagnosed at age 82
Brother with a head and neck cancer diagnosed in his forties

Social History:
The patient is a veteran with a 20 pack year history and continued tobacco use. He has a history of alcoholism but has been sober since 2004. He has one adult son.

Review of systems:
The patient reported severe tenderness of the left nipple, although improved over the past month prior to presentation. He denied weight loss, fatigue, and fevers.

Physical Examination:
Left nipple was retracted with induration of the surrounding skin. The nipple had an overlying heme-crusted friable plaque. The nipple and surrounding 3cm of skin were very tender to light touch. The right chest and nipple are normal. There is no axillary or cervical lymphadenopathy.

Laboratory Data/Diagnostic Procedures and Tests:
08/08 Computed tomography, chest: 2cm mass present just inferior to nipple-areolar complex; no intrathoracic lesions noted.

Histopathology:
07/08 Left nipple: Sections of partially eroded skin show infiltrating dermal proliferation of cords of monomorphic epithelial cells. Some are arranged in single filing. Many of these cells have enlarged nuclei, hyperchromatic chromatin, and focal intracytoplasmic mucin.

Diagnosis:
Male invasive adenocarcinoma of the breast

Treatment and Course:
The patient was referred to surgical oncology and underwent a simple left mastectomy and sentinel lymph node biopsy that showed mixed ductal and lobular mammary carcinoma. One out of two sentinel nodes were positive with evidence of metastasis, showing extracapsular and extranodal extension. He

subsequently had eight additional lymph nodes removed in a complete axillary dissection, all of which were clear of malignancy. Immunostaining of the breast tissue showed that 20% of the invasive tumor nuclei stained positive for estrogen receptor antibody and 90% stained positive for progesterone receptor antibody. A plan for future adjuvant therapy has not yet been established.

Discussion:

Male breast cancer (MBC) is extremely rare, accounting for less than 1% of all male cancers and 1% of total breast cancers yearly in the United States. Initial presenting symptoms may include nipple retraction, nipple ulceration or bleeding, discharge and pain. In several prospective and retrospective studies, potential risk factors for development of MBC have been identified including obesity, testicular abnormalities, infertility, Klinefelter's syndrome and a family history. Smoking and alcohol have shown inconsistent results as potential risk factors. In female breast cancer (FBC) there is a known increased risk with both BRCA 1 and BRCA 2 gene mutations. In MBC the correlation with BRCA 1 is less established although there is a known increased risk with BRCA 2 gene.

Compared to females, men tend to present with later stage disease with over 40% showing stage III or IV disease at diagnosis. MBC presents with larger tumors, more lymph node positivity and higher grade tumors. This is likely related to delay in diagnosis. In a large comparative analysis of the veteran affairs' population, FBC and MBC patient and disease characteristics were evaluated. The mean age of diagnosis for MBC was 67 years old versus 57 years old for FBC, with median survival at 7 years for men and 9.6 years for women. Overall survival with stage I or II disease was lower for men, although no difference was found in overall survival between men and women with stage III or IV disease. There were also significant differences in the tumors themselves. The most common male histology is ductal carcinoma, with lobular carcinoma being very infrequent. There is also a larger percentage of MBC tumors that are estrogen receptor positive. In FBC estrogen receptor (ER) positivity is correlated with improved survival and response to hormone therapy. However, ER positivity may not have the same correlation in MBC, with tumors not responding as well to standard therapy of tamoxifen and showing increased proliferative activity. Even with equivalent use of tamoxifen in patients with ER positive tumors, males had a lower survival rate compared to females.

For localized disease, as with females, modified radical mastectomy is recommended with sentinel node biopsy and axillary dissection depending on clinical node involvement. There have been no randomized control trials to evaluate the efficacy of adjuvant therapy in MBC so current treatments are based on studies from FBC. Radiation therapy can decrease local recurrence but does not appear to change overall survival. There is improved survival with tamoxifen therapy in ER positive tumors and a 5 year treatment regimen is recommended. In patients with ER negative tumors doxorubicin based therapies are often used.

Essential Lessons:

- Male breast cancer is a rare disease and diagnosis is usually delayed.
- Due to its rarity, the treatment options for male breast cancer are less well defined.

References:

1. Brinton LA, Richesson DA, Gierach GL, et al. Prospective evaluation of risk factors for male breast cancer. *J Natl Cancer Inst* 2008; 100(20): 1477-81.
2. Hahn K. Chapter 21: Special Issues in Breast Cancer Management *in* MD Anderson Manual of Medical Oncology. Kantarjian HM editor in chief. http://www. accessmedicine.com/content.aspx? aID =2791929.
3. Nahleh ZA, Srikantiah R, Safa M, et al. Male breast cancer in the veteran's affairs population: a comparative analysis. *Cancer* 2007; 109(8): 1471-77.
4. Agrawal A, Ayantunde AA, Rampaul R, Robertson JF. Male Breast Cancer: a review of clinical management. *Breast Cancer Res Treat* 2007; 103(1): 11-21.

Case # 4

Case Presented by Caroline Schmitt, MD, Anthony J Mancini, MD and Michelle Bain, MD

History of Present Illness:
This 13 month old female presented at age 7 months with an eight week history of "little bumps" that started on her chest, spread to her back, and then erupted to a generalized distribution, including the labia. She was diagnosed with milia at an outside institution and treated with nonsteroidal emollients without improvement.

Past Medical History:
Full-term infant; otitis externa, right ear

Medications:
Neomycin otic drops

Allergies:
No known drug allergies

Family and Social History:
The patient's parents are from India and she has one healthy older brother.

Review of systems:
The patient has no history of fevers, diarrhea, vomiting, irritability, or polyuria; she is gaining weight and meeting milestones appropriately.

Physical Examination:
In a generalized distribution are innumerable 1-2.5 mm hypopigmented to pinkish opaque dermal papules, most prominent on the back and labia majora. The scalp and flexural areas are relatively spared.

Laboratory Data:
The following were positive or abnormal:
White blood cell count 19.3 k/uL (6.0-18.0) and absolute neutrophil count 8.8 k/uL (1.5-6.3).

The following were negative or within normal limits:
Complete metabolic panel, hemoglobin, platelets, coagulation profile, urinalysis, and hematologic chromosome analysis.

Diagnostic Procedures and Tests:

6/30/08	Bone survey of the spine, pelvis, hips, skull, hands, and legs: within normal limits
7/08/08	Magnetic resonance imaging without contrast, abdomen and pelvis: Transverse 2-bright multifocal hepatic nodularity
7/10/08	Ultrasound, abdomen: liver shows a diffuse micronodular infiltrative process
7/10/08	Radiograph, chest: no evidence of intrathoracic abnormality
7/25/08	Computed tomography, head: soft tissue mass causing destruction of the right lateral orbital wall/greater wing of the sphenoid bone, measuring 3 x 1.3 x 2.1 cm. There is mass effect on adjacent intraorbital structures; no intracranial extension is definitively identified.
7/29/08	Bone scan: Focal activity in the sphenoid wing extending into the lateral right orbit

Histopathology:

06/08	Back: Biopsy shows both intraepidermal and superficial dermal nests of epithelioid cells with increased amounts of pale-staining cytoplasm and reniform nuclei. These cells stain positive for CD1a.

Diagnosis:
Langerhans cell histiocytosis

Treatment and Course:
The patient was referred to oncology at Children's Memorial Hospital for systemic chemotherapy to treat her multisystem Langerhans cell proliferative disorder involving the skin, liver, and skull. A bone marrow biopsy was performed, excluding myelogenous involvement, and a venous access port was placed. The patient began receiving prednisolone and vinblastine according to the LCH III protocol established by the Histiocyte Society. Follow-up abdominal ultrasound did not redemonstrate the liver nodules and repeat head CT after nine weeks' interval showed a slight decrease in the size of the destructive right orbital mass without intracranial extension. The patient was referred to ophthalmology for evaluation of functional impairment of the right eye and was found to have mild proptosis without visual defect. Her cutaneous involvement, although initially responsive to chemotherapy, flared subsequently, and at follow-up the patient had classic scalp involvement consisting of crusted red-brown coalescent papules. She is presently being treated with low potency topical steroids.

Discussion:
Langerhans cell histiocytosis (LCH) is a rare proliferative clonal disorder of Langerhans cells of uncertain primary etiology affecting 0.5-5.4 people per million per year. LCH is comprised of a diverse spectrum of clinicopathologic presentations, from aggressive to spontaneously involuting, from unifocal to disseminated. The most common sites of involvement are the skin and bone, but LCH can also affect the lymphoid organs, mucosae, gastrointestinal tract, lungs, liver, and central nervous system. 50-80% of patients have cutaneous involvement, making dermatologists key players in diagnosis and management.

The classic nomenclature to describe LCH (e.g. Hand-Schuller-Christian disease, Letterer-Siwe disease) was revised once it was established that the CD45, S100, and CD1a positive, and CD14 and Factor XIIIa negative Langerhans antigen presenting cell is the predominant cell type in all forms of the disease. The present classification divides LCH first into single or multi-organ disease and then, if multi-organ involvement is present, a further distinction is made based on the presence or absence of organ dysfunction. The clinical stratification then dictates therapeutic decisions. Limited cutaneous disease often requires no therapy, while multi-agent chemotherapy is indicated for multi-organ disease. Poor prognostic indicators are young age at presentation; involvement of the spleen, liver, lungs, or hematopoietic system; and the presence of widely disseminated disease and organ dysfunction. A highly favorable prognostic indicator is response to chemotherapy during the six week induction phase, with good responders having an 88-91% survival rate compared to 17-34% for nonresponders. That this patient showed radiographic improvement in her LCH and lacked evidence of any organ dysfunction, despite having multisystem organ (including liver) involvement, portends a guardedly favorable prognosis.

Essential Lessons:
- Clinicopathologic presentation of LCH varies from benign, self-limited, localized disease to potentially fatal multisystem disease.
- Prognosis in multisystem disease depends on the number and extent of organ systems involved and early response to chemotherapy.

References:

1. Favara, et al. Contemporary classification of histiocytic disorders. The WHO Committee On Histiocytic/ Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. *Med Pediatr Oncol* 1997; 29 (3):157-66.
2. Histiocytosis Association of America. <http://www.histio.org> accessed 2 Nov 2008
3. Satter EK, High WA. Langerhans cell histiocytosis: a review of the current recommendations of the Histiocyte Society. *Pediatr Dermatol* 2008; 25 (3): 291-5.

Case # 5

Case Presented by Marie Reichle, MD
and Iris Aronson, MD

Patient A

History of Present Illness:
This 52 year old Hispanic female presented to our clinic in October of 2004 with a one and a half year history of bilateral ocular discomfort. Symblepharon had been diagnosed by an outside ophthalmologist. She denied any vesicles in her mouth, nose, or on the skin. She reported a constant burning sensation in her eyes, a foreign body sensation, and photophobia. Prior treatments included various ophthalmic drops and doxycycline.

Past Medical History:
Osteoporosis, arthritis, and anemia

Past Surgical History:
Complete hysterectomy in 1997 and bilateral radial keratotomy in 1990

Medications:
Ferrous sulfate and multivitamin

Allergies:
Tetracaine ophthalmic

Family History:
Her mother had rheumatoid arthritis. No family history of malignancy.

Review of systems:
The patient reported photophobia, eye pain, and poor vision. She denied oral ulcers, nasal ulcers, dysuria, vaginal pain, rectal pain, recent illness, fevers, chills, or weight loss.

Physical Examination:
Currently, there is scleral injection bilaterally, eyelid erythema, surgical absence of upper eyelashes, fornix foreshortening, and lateral symblepharon. Significant effort is required to open her eyes a few millimeters.

Laboratory Data:
The following were negative or within normal limits:
Complete blood count, complete metabolic panel, antinuclear antibody, rheumatoid factor, total hemolytic complement, CA 125, and glucose-6-phosphate dehydrogenase.

Histopathology and Immunopathology:
10/04 H&E, left lower eyelid conjunctiva: Sections of the biopsy show subepithelial clefting with a mixed inflammatory cell infiltrate including lymphocytes, plasma cells, and neutrophils. There is also increased fibrosis in the lamina propria.
10/04 Direct immunofluorescence, left lower eyelid conjunctiva: At the basement membrane zone, there is thick linear fibrin staining, speckled C3 staining, and a focal linear area of IgG staining.
09/08 Indirect immunofluorescence: On saline split skin, there is very weak staining on the dermal side with IgG.

Diagnosis:
Cicatricial pemphigoid

Treatment and Course:
Numerous medications have been used to treat this patient including: prednisone, cyclophosphamide (oral and intravenous), dapsone, azathioprine, intravenous immunoglobulin (IVIG), mycophenolate mofetil, etanercept, methotrexate, and infliximab with methylprednisolone. Her inflammation has continued despite these treatments. Currently, initiation of rituximab with IVIG is planned. Work up for malignancy including upper endoscopy, colonoscopy, mammography, and chest radiography has been normal to date.

Over the course of her disease, her eyelashes have been removed multiple times due to trichiasis. Her right eye required amniotic membrane grafting and overlay. While living in Mexico, a left corneal perforation prompted a corneal transplant. The graft was rejected due to intense inflammation. Currently, she is completely blind in her left eye with severely limited sight in her right eye. Documented visual acuity of the right eye was 20/200 and of the left eye was 20/400 in October 2008.

Patient B
History of Present Illness:
This patient is a 75 year old female who presented to our clinic in March of 2008 with complaints of painful oral and genital erosions. She denied eye symptoms.

Past Medical History
Hypothyroidism

Past Surgical History:
Partial hysterectomy

Medications:
Levothyroxine

Allergies:
No known drug allergies

Family History:
Negative for malignancy, skin diseases, or autoimmune diseases

Review of systems:
She reported a sore throat and dysphagia. She denied fevers, arthralgias, myalgias, and weight loss.

Physical Examination:
There were punched-out, erythematous ulcerations on the bilateral buccal mucosae, ventral tongue, and hard palate. The presacral skin had multiple hyperpigmented, minimally scaly papules, some with central erosions. The left labia majora had an erythematous erosion.

Laboratory Data:
The following were positive or abnormal:
CA 125 2,262 U/ml (0-35), antinuclear antibody titer 1:1280 (<1:40), erythrocyte sedimentation rate 38 mm/hr (0-20), total protein 8.4 g/dl (6-8).

The following were negative or within normal limits:
Complete blood count, complete metabolic panel, total hemolytic complement and antibodies to double stranded DNA, single stranded DNA, Smith, SSA (Ro), SSB (La), and ribonucleic protein.

Diagnostic Procedures and Tests:

08/08 Rigid laryngoscopy with videostroboscopy: There is hyperemia of the true vocal folds and cicatrix at the interarytenoid region causing slight impairment of airway function. There is diffuse mucosal thickening and probable scarring of the posterior pharyngeal wall and glottic folds.

Histopathology and Immunopathology:

04/08 H&E, oral mucosa: Sections of the biopsy show subepithelial clefting with mixed inflammatory cell infiltrate. There is slightly increased fibrosis in the lamina propria. The overlying epithelium is hyperplastic with parakeratosis.

04/08 Direct immunofluorescence, sacral skin: There is positive linear staining at the basement membrane zone with IgG and C3.

04/08 Indirect immunofluorescence: There is positive linear staining with IgG at the basement membrane zone at a 1:160 titer and on the dermal side of saline split skin.

11/08 IgG_4 anti-laminin-332 enzyme-linked immunosorbent assay: Pending

Diagnosis:

Cicatricial pemphigoid

Treatment and Course:

The patient was started on doxycycline 100 mg twice daily. During her malignancy work-up, she was noted to have an extremely elevated CA 125. Shortly thereafter, she was hospitalized for shortness of breath, and a thoracentesis revealed ovarian cancer cells. She started chemotherapy at Rush Hospital and underwent an oophorectomy. She suffered from a pulmonary embolism and was started on anticoagulation. She later developed hoarseness and shortness of breath. Rigid laryngoscopy revealed cicatricial pemphigoid involvement of the pharynx and larynx. Treatment options were limited due to ongoing chemotherapy and risk of myelosuppression, so she was started on prednisone 15 mg daily. Since her last visit to our clinic in July 2008, she has been hospitalized repeatedly at Rush. She has undergone a tracheotomy, developed steroid myopathy, and was most recently hospitalized for shortness of breath likely secondary to malignant ascites.

Discussion:

Cicatricial pemphigoid (CP) is an acquired autoimmune bullous disease in which autoantibodies target autoantigens in the basement membrane zone (BMZ). Vesiculobullous lesions and erosions occur predominately on mucous membranes but can also involve skin. The burden of this disease can be great due to pain from local inflammation, and such sequelae as esophageal strictures, blindness, and airway compromise. CP is fortunately rare with an incidence between 1 in 12,000 to 1 in 20,000 in the general population. People commonly affected are between 60 and 80 years of age, and the female to male ratio is about 2:1.

Immunofluorescence studies are integral in diagnosing autoimmune bullous diseases. If BMZ antibody staining is seen on direct immunofluorescence (DIF), indirect immunofluorescence (IIF) using saline split skin (SSS) substrate may be performed. Depending on the targeted autoantigen, predominant staining occurs on either the epidermal or dermal side of the split. The differential diagnosis for IgG staining only on the dermal side of SSS includes epidermolysis bullosa acquisita, p200 pemphigoid, p105 pemphigoid, and antiepiligrin cicatricial pemphigoid (AECP).

In AECP, autoantibodies target laminin 332, previously known as laminin 5 or epiligrin. Some patients with AECP also have autoantibodies against laminin 311 (previously known as laminin 6). The AECP subgroup is unique due to its association with solid tumor malignancy, as it has been reported that up to 29% of patients with documented diagnosis of AECP develop solid malignant tumors, with a relative risk of 15.4 within the first year after blister onset. Adenocarcinomas are the most commonly associated

malignancies. Non-Hodgkin's lymphoma, ovarian cancer, and cutaneous T-cell lymphoma have also been reported. The association between AECP and cancer has enhanced the need to identify seropositive patients. Unfortunately, AECP patients cannot be differentiated from other CP patients on clinical grounds alone. IIF performed on SSS substrate showing dermal staining suggests the diagnosis of AECP. However, IIF has a low sensitivity in testing CP patients' autoantibodies and therefore is not conclusive. Radioimmunoassay is a more sensitive test to detect anti-BMZ antibodies. Testing specifically for anti-laminin-332 autoantibodies may be performed by immunoprecipitation, immunoblotting, or by a new enzyme-linked immunosorbent assay (ELISA). This IgG4 ELISA has a reported sensitivity of 91% and specificity of 98%. With an estimated 5 to 20% of all CP patients having anti-laminin-332 antibodies, a readily available ELISA test could someday become key in identifying this group of patients that need extensive evaluation for malignancy.

Adequate treatment of CP is essential to avoid permanent tissue damage. Systemic corticosteroids can quickly reduce inflammation during the initiation of immunosuppression. Severe and progressive disease should be treated with cyclophosphamide due to its high success rate. Other treatments for CP include dapsone, tetracyclines (with or without nicotinamide), sulfapyridine, azathioprine, mycophenolate mofetil, methotrexate, thalidomide, IVIG, plasmapheresis, etanercept, and infliximab.

Rituximab is an anti-CD20 antibody that has been extremely successful in treating a variety of autoimmune bullous diseases. Recently, there have been reports of using rituximab for the treatment of CP. Taverna et al. reported a 22 year old male with CP refractory to other treatments whose disease was well controlled with rituximab in combination with mycophenolate mofetil and prednisone. On the contrary, Schmidt et al. reported a case of CP whose ocular disease was not able to be controlled with rituximab, and the patient ultimately developed blindness. There is limited and mixed data regarding rituximab's efficacy in treating CP, and further observations and studies are needed to better describe its utility.

Essential Lesson:

- Antiepiligrin cicatricial pemphigoid patients have a greatly increased risk of cancer (relative risk 15.4).
- Malignancy screening is key when evaluating patients who may have antiepiligrin cicatricial pemphigoid.

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Case # 6

Presented by Platina E. Coy Gershtenson, MD, Aaron Cetner, MD and Claudia Hernandez, MD

UNKNOWN CASE

A 14 month old female born at 36 weeks with congenital gastroschisis and volvulus required a small bowel resection with resultant short gut syndrome. She was evaluated by dermatology for a sudden eruption of compressible, erythematous, blanchable papules surrounding the abdominal scar.

Case # 7

Case Presented by Jonathan Pewitt, MD, John L. Villano, MD and Aleksandar L. Krunic MD, PhD

History of Present Illness:
This is a 74 year old Caucasian female with a five year history of refractory keratoacanthoma centrifugum marginatum. Prior to her presentation to our department in 2006 the patient had undergone unsuccessful wide surgical excision, Mohs surgery, chemotherapy, radiation, systemic retinoids, and full-thickness debridement of the scalp and bilateral helices. She received a 6 month course of oral methotrexate, 15mg weekly, which led to partial plaque resolution until systemic methotrexate was discontinued due to concerns about toxicity. Intralesional methotrexate was then started although she failed to respond and her scalp plaques reappeared. Even with her extensive skin involvement, on multiple occasions she failed to demonstrate metastatic disease on positron emission tomography, computed tomography, or magnetic resonance imaging.

Past Medical History:
Hypertension, hyperlipidemia, lumbar and thoracic vertebrae fractures, chronic parotid gland sialoadenitis, left facial nerve neuritis with resultant palsy, and left eye ectropion

Medications:
Lisinopril, atorvastatin, pilocarpine, diazepam, calcium citrate, and ibuprofen

Allergies:
Penicillin, clindamycin, bacitracin, and acitretin

Social History:
The patient is retired. She has a 53 pack year history of smoking.

Review of systems:
The patient reports having occasional loose stools, a pruritic rash on her arms, upper back and chest, and increased dry skin. She denies fever, chills, nausea, vomiting, fatigue, or shortness of breath.

Physical Exam:
Examination reveals thin crusted plaques along the mid-frontal and left temporal scalp at the remaining hair line. Large moist, pink plaques are present at the occiput and right posterior auricular area. The right temple has a large, moist, pink, cribiform erosion. The vertex scalp has exposed yellow-brown bone with islands of telangiectatic erythematous shiny skin growing into the area. The surrounding scalp is smooth, shiny and slightly atrophic in areas. Inferior to the right lateral canthus there is a yellow nodule with scattered smaller white papules over the right zygoma. She has ectropion of the left lower eyelid with mild conjunctival injection and tearing. The patient's upper trunk and extremities reveal few scattered excoriated erythematous papules and rare pustules.

Histopathology:

04/05-11/06	There is an exo-endophytic lesion with hyperkeratosis, parakeratosis, and scale crust.
5 reviewed	There is extensive epidermal hyperplasia with proliferation of well-differentiated nests of squamous cells. Mild cytologic atypia is present. Dilated blood vessels and a perivascular infiltrate of lymphocytes and eosinophils are seen in the dermis.
06/05	Posterior neck: EGFR staining is moderate to strongly positive (2-3+) in the basal layers with prominent membrane staining.

09/08 Left forearm: Spongiotic subcorneal pustulosis with superficial perivascular mixed inflammatory cell infiltrate of neutrophils, lymphocytes and histiocytes. There is mild dermal edema. PAS is negative.

Diagnosis:
Keratoacanthoma centrifugum marginatum

Treatment and Course:
On July 15, 2008, the patient was started on 150 mg of oral erlotinib daily. To date, she has developed no new lesions, and existing lesions have regressed. After initiation of erlotinib she developed a new papulopustular rash on her upper trunk and arms that has now partially resolved.

Discussion:
Keratoacanthoma centrifugum marginatum (KCM) is an uncommon variant of keratoacanthoma, characterized by progressive peripheral expansion and concomitant central clearing. KCM responds to a number of treatments, including intralesional and oral methotrexate, topical 5-fluorocuracil, Mohs surgery, intralesional bleomycin, and oral retinoids. Epidermal growth factor receptor (EGFR) inhibitors represent an additional treatment option for resistant squamous cell neoplasms.

EGFR, a transmembrane glycoprotein, is a member of the tyrosine kinase family. EGFR regulates cell growth and differentiation. The EGFR distribution pattern in normal skin depends on the differentiation state of the keratinocyte. Normal skin shows some cytoplasmic staining, strong cell membrane staining of the stratum basale and lower stratum spinosum, and gradual weakening in the upper stratum spinosum. Benign and malignant neoplasms of the skin derange this pattern and over-expression of EGFR leads to increased cell proliferation and neoplasm formation. This abnormal expression, which occurs in many solid tumors, provides a target for therapy. Monoclonal antibodies directed against the extracellular domain of EGFR (panitumumab, cetuximab) or small molecule inhibitors of the intracellular tyrosine kinase domain (erlotinib, gefitinib) block the tumor cell cycle and decrease neoplastic growth.

EGFR inhibition results in impaired growth and migration of keratinocytes and inflammatory cell recruitment leading to injury of the papillary dermis and epidermis. EGFR inhibitors are associated with class-specific cutaneous side effects, including acneiform eruptions, paronychia, hyperpigmentation xerosis, trichomegaly, and telangiectasia formation. The acneiform eruption, which occurs in more than 50% of cases, consists of erythematous papules and pustules in a distribution similar to acne vulgaris. The presence and severity of the rash has been used to gauge the response to therapy and may be a positive predictor of survival when used for invasive squamous cell carcinoma.

Essential Lessons:
- EGFR inhibitors can provide a therapeutic option for resistant squamous proliferations.
- Acneiform eruptions are a common side effect and are predictive of the efficacy of EGFR inhibitors.

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Case # 8

Case Presented by Rikk Lynn, MD
and Lawrence Chan, MD

History of Present Illness:
This 9 year old boy presented with a new onset rash. According to the patient's mother, he had begun developing thickening of the skin over his palms and soles two weeks prior to presentation. He then developed an erythematous rash over his face, trunk, and extremities. Of note, a few days prior to the onset of the rash, the patient had diffuse joint pains and flu-like symptoms. The patient initially was treated by an outside physician with fluocinonide ointment with no improvement.

Past Medical History:
The patient was born of a full-term pregnancy with normal spontaneous vaginal delivery.

Medications:
Fluocinonide 0.05% ointment

Allergies:
No known drug allergies

Family History:
The patient's father has a history of mild psoriasis

Review of systems:
The patient had subjective fevers, vomiting and diffuse joint pains.

Physical Examination:
The patient has confluent erythema extending from his scalp to the upper trunk. There are multiple perifollicular erythematous papules with central keratotic spines diffusely over his upper arms, trunk, buttocks, and upper legs. The palms and soles have a thick, hyperkeratotic waxy appearance with some mild fissuring.

Laboratory Data/Diagnostic Procedures and Tests:
None

Histopathology:
07/08 Right buttock: Biopsy shows a slightly irregular psoriasiform epidermal hyperplasia associated with a superficial dermal perivascular infiltrate of lymphocytes. There is alternating parakeratosis and orthokeratosis with a checkerboard appearance.

Diagnosis:
Juvenile pityriasis rubra pilaris

Treatment and Course:
After presentation to our clinic, the patient was started on tazarotene 0.05% cream nightly, triamcinolone 0.1% ointment to the trunk and extremities, and hydrocortisone 2.5% ointment to his face. After little improvement with this regimen, the patient was started on isotretinoin 10mg by mouth daily. This was increased to 20mg after two weeks, but had to be discontinued as the patient experienced increased aggression, agitation, and excessive drying of his skin. The patient's mother then tried emu oil, which had been suggested from multiple online support group contacts. Emu oil was applied once to twice daily to the affected areas and the patient noted rapid improvement. He now applies emu oil on an as needed basis and is off all other treatments with continued resolution.

Discussion:

Pityriasis rubra pilaris (PRP) exhibits a bimodal distribution of age onset, with the first peak in early childhood and the second after the fifth decade. In children, onset has frequently followed trauma or an infection. Overall, at least three-fourths of cases will resolve within three months to seven years of onset. Most pediatric cases clear within three and a half years and relapses are uncommon but may occur. PRP affects males and females in equal frequency and the incidence of PRP has been reported to be 1 case in 3500-5000 patients presenting to dermatologic clinics in the United States.

The classical presentation consists of erythematous hyperkeratotic patches and plaques above the waistline. New lesions begin as follicular hyperkeratosis which may then coalesce. The eruption progresses in a cephalocaudad direction with more extensive involvement of the seborrheic areas initially. The dermatosis often generalizes, leaving only "skip areas" or islands of sparing which are very characteristic of erythrodermic PRP. A dense palmoplantar keratoderma (PPK) is one of the hallmarks of PRP.

PRP is usually divided into five classes: type I, classical adult; type II, atypical adult; type III, classic juvenile; type IV, circumscribed juvenile; and type V, atypical juvenile. The type III, classic juvenile form represents 10% of cases and most closely resembles the classic adult form. The circumscribed juvenile form (type IV) is the most common in children making up about 25% of cases. Sharply circumscribed hyperkeratotic papules, usually forming an erythematous plaque, on the elbows and knees develop insidiously in association with PPK and occasionally superficial papulosquamous lesions develop elsewhere. Typically these patients do not develop generalized disease.

Because childhood PRP has a good prognosis for spontaneous resolution, aggressive therapies should be reserved for disabling, treatment-resistant, or chronic cases. The oral retinoids have been effective in PRP, showing response rates within four weeks and marked improvement or clearing in 4-7 months. The isotretinoin dose used is approximately 1-1.5 mg/kg/day. Acitretin is also beneficial in the treatment of PRP. The effect of retinoids on familial PRP appears less certain. Other therapies include methotrexate, azathioprine, corticosteroids, cyclosporine, or infliximab with variable success. Although UV light therapy runs the risk of exacerbating the disease, there have been reports of success with UVB, UVA1, and PUVA. In this case, the patient could not tolerate isotretinoin; however, topical emu oil application resulted in considerable improvement of his skin manifestations. Whether this was related to the therapeutic effects of emu oil, or the spontaneous resolution of disease is not known. Emu oil is made from the fat of the emu, a bird native to Australia. The oil is approximately 70% unsaturated fatty acids. The largest component is oleic acid. Emu oil also contains about 20% linoleic acid and 1-2% linolenic acid. To date, there have been no studies evaluating the efficacy of emu oil for the treatment of PRP.

Essential Lessons:

- Childhood onset PRP is rare, but its presentation is dramatic.
- If possible, conservative treatments should always be tried first.
- Emu oil could be a potential therapeutic option.

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Case # 9

Case Presented by Tarun Kukreja, MD and Lawrence Chan, MD

Patient A

History of Present Illness:
This 58 year old African American male presented with hypopigmented spots and bumps on his back, chest, and arms of several years duration. The patient had been taking hydroxychloroquine sporadically with partial resolution of the spots, but had to discontinue treatment in 2007 due to elevated liver function tests. Since the discontinuation of hydroxychloroquine, the patient's skin lesions recurred. The patient was then treated with topical triamcinolone 0.1% ointment and tacrolimus 0.1% ointment for a few months with minimal resolution. The patient has no history of shortness of breath or other pulmonary symptoms.

Past Medical History:
Sarcoidosis, hypertension, hyperlipidemia, and diabetes mellitus

Medications:
Amlodipine, atenolol, haloperidol, minocycline, and rosuvastatin

Allergies:
No known drug allergies

Review of systems:
The patient denies any fevers, chills, night sweats, weight loss, vision changes, dyspnea on exertion, or joint pains.

Physical Examination:
The face, bilateral arms, back and trunk have many hypopigmented patches and papules with some coalescing into larger polycyclic plaques, many with central repigmentation. There is no regional lymphadenopathy.

Laboratory Data:
The following were negative or within normal limits:
Complete blood count and complete metabolic panel.

Diagnostic Procedures and Tests:
2/07 Radiograph, chest: Focal linear fibrosis in the upper lung fields bilaterally consistent with old granulomatous disease.

Histopathology:
2/08 Left arm: Biopsy shows a superficial and deep multi-nodular granulomatous infiltrate sparing the epidermis. The granulomas are predominantly composed of epithelioid histiocytes with a few sprinkled lymphocytes. The special stains for microorganisms are all negative.

Diagnosis:
Hypopigmented sarcoidosis

Treatment and Course:

The patient states that all hypopigmented areas have begun to repigment and flatten since starting treatment in April 2008 with minocycline 100mg twice daily.

Discussion:

Sarcoidosis is a granulomatous disease with a chronic course. The clinical manifestations of the disease are variable. Most commonly, patients present with reddish-brown to violaceous papules and plaques but the morphology may include annular, psoriasiform, nodular, ichthyosiform, verrucous, atrophic, and hypopigmented variants. Darker skin types more frequently display atypical presentations, including hypopigmentated patches.

Oral corticosteroids are accepted as the most effective treatment for sarcoidosis, but have many well-described side effects and are not generally used in cutaneous sarcoidosis. Several studies have shown success with antimalarials including chloroquine and hydroxychloroquine. Unfortunately, not all patients may respond to this group of medications and side effects are not uncommon.

Minocycline and doxycycline have been shown to be effective in the treatment of cutaneous and systemic sarcoidosis. They have also been successful in other granulomatous dermatoses such as silicone-induced granulomas and granulomatous cheilitis. In our patient, significant clearance of most hypopigmented areas was noted within a few months upon starting minocycline.

Minocycline has been shown to inhibit T-cell proliferation as well as granuloma formation in vitro. It is still being debated within the medical community whether the therapeutic effect of the tetracyclines on sarcoidosis results from their anti-infectious abilities or their anti-inflammatory and immune modulating properties. Recent studies point to the presence of DNA products specific for mycobacteria and propionibacterial species in the lymph nodes of patients with sarcoidosis. Nevertheless, minocycline is a potentially effective agent for the treatment of sarcoidosis with a favorable risk profile.

Essential Lessons:

- Hypopigmented sarcoidosis is a rare but dramatic cutaneous manifestation of sarcoidosis.
- Minocycline is a potential therapeutic option with a favorable side effect profile for cutaneous sarcoidosis.

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Case # 9

Case Presented by Tarun Kukreja, MD and Milena Lyon, MD

Patient B

History of Present Illness:
This 31 year old African American female presented with a rash in her bilateral axillae for approximately 1 year. She reports the lesions appeared immediately after shaving with someone else's razor. The lesions are asymptomatic and relatively stable. She presented to clinic because they were not resolving.

Past Medical History:
Sarcoidosis (positive lymph node biopsy at 12 years of age) and anterior uveitis

Medications:
Prednisolone acetate eye drops

Allergies:
No known drug allergies

Family History:
Aunt with sarcoidosis and systemic lupus erythematous

Review of systems:
The patient recently developed dyspnea with exertion. She denies any fevers, chills, night sweats, or joint pains.

Physical Examination:
In the bilateral axillae there are multiple hyperpigmented to violaceous papules. Some papules coalesce to form plaques.

Laboratory Data:
The following were negative or within normal limits:
Complete blood count and basic metabolic panel.

Diagnostic Procedures and Tests:
09/07 Pulmonary Function Tests: decreased diffusion capacity

01/08 Computed tomography, chest: Fibrotic change and septal thickening is identified in the bilateral lung bases, consistent with a history of sarcoidosis. Multiple nonspecific pulmonary densities are seen in the bilateral lungs possibly related to sarcoid.

Histopathology:
02/08 Left axilla: Biopsy shows a superficial and deep multinodular granulomatous infiltrate. The infiltrate is composed mostly of epithelioid histiocytes with a minor component of lymphocytes. Special stains for fungi and mycobacteria are negative.

Diagnosis:
Sarcoidosis with cutaneous involvement

Treatment and Course:
The patient was started on triamcinolone 0.1% ointment to the axillary lesions with minimal improvement. Subsequently she developed pulmonary disease necessitating oral prednisone which she reports has greatly improved her cutaneous lesions.

Interestingly, her only disease manifestation since diagnosis at the age of 12 had been anterior uveitis until this past year when she developed cutaneous and pulmonary disease.

Discussion:
Cutaneous sarcoidosis can be seen in areas of obvious or trivial trauma. It has been reported to arise at sites of tattoos, prior scars or venipuncture sites, and previous folliculitis. Foreign bodies or other antigens introduced into the dermis by injury may provide a stimulus for granuloma formation in a patient predisposed to sarcoidosis. It has been stated that immune dysfunction may result from an antigen that is not fully cleared by the immune system, creating a chronic T helper 1 (Th1) response which then leads to granuloma formation. The antigens that could induce this response may be infectious, environmental, or autoantigens.

Polarizable foreign bodies are not uncommonly found in the granulomatous cutaneous lesions of patients with systemic sarcoidosis, and do not exclude the diagnosis of sarcoidosis. Thus it has been suggested that patients with 'sarcoidal' or granulomatous type skin lesions should be evaluated for the presence of systemic sarcoidosis regardless of whether a foreign-body is present on skin biopsy.

We present this patient for clinical interest as a unique manifestation of cutaneous sarcoidosis in a patient with systemic disease.

Essential Lessons:
- Cutaneous sarcoidosis can develop in areas of previous trauma regardless of how trivial.
- The presence of foreign bodies in granulomatous skin lesions should prompt a work up for systemic sarcoidosis.

References:

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Case # 10

Case Presented by Tanya Bulj-Stevens, MD, Lawrence Chan, MD and Iris Aronson, MD

History of Present Illness:
This 73 year old woman with an eight month history of itchy urticarial papules and plaques presented to our clinic in November 2007 after developing a generalized eruption of tense hemorrhagic and clear blisters. The results of direct and indirect immunofluorescence studies were consistent with bullous pemphigoid. She was initially treated by an outside dermatologist with tetracycline and high dose prednisone. Upon presentation to our clinic, mycophenolate mofetil was initiated and the prednisone was tapered. She achieved full remission within six weeks of treatment with mycophenolate mofetil. Over the course of nine months, she remained clear of blisters but reported a flare in August 2008.

Past Medical History:
Hypertension, tic douloureux, and osteoporosis

Medications:
Doxycycline, mycophenolate mofetil, cetirizine, prednisone, carbamazepine, calcium, vitamin D, alendronate sodium, multivitamin, lisinopril, hydrochlorothiazide, and aspirin 81mg once daily

Allergies:
No known drug allergies

Review of systems:
She complained of persistent pruritus, fatigue, and insomnia. She denied dysphagia or hoarseness.

Physical Examination:
The patient presented with multiple tense bullae involving 60% of her body surface area. The bullae were on average 1-5 cm in size and primarily located on the palms, soles, thighs, arms, lower legs, and less so on the abdomen, chest and back. Approximately 30% of the bullae were hemorrhagic. Interspersed among tense hemorrhagic and clear bullae were many bright red erosions, some with serosanguinous discharge and some with an overlying hemorrhagic crust. There were extensive erythematous papules coalescing into large edematous plaques mainly on the lower back, abdomen and less so on the arms and legs. There was no ocular, nasal, or oral mucosal involvement.

Laboratory Data:
The following were negative or within normal limits:
Platelet count and complete metabolic panel except for chronic hyponatremia

Histopathology and Immunopathology:
Studies to screen for the diagnosis of bullous pemphigoid:

11/07 H&E, left thigh (edge of blister): Biopsy shows subtle subepidermal clefting with a superficial and mid-dermal perivascular and interstitial infiltrate of lymphocytes and numerous eosinophils (this biopsy specimen was originally intended for DIF).

11/07 Direct immunofluorescence, left thigh (lesional skin): Linear deposition of IgG and C3 at the epidermal basement membrane zone. The specimen was sectioned and stained with H&E and revealed numerous red blood cells within the blister cavity.

11/07 Indirect immunofluorescence: On saline split skin, staining on the epidermal (roof) side with IgG

11/07 Indirect immunofluorescence: Linear IgG binding to epithelial basement membrane at 1:320 titer

08/08 Indirect immunofluorescence: Linear IgG binding to epithelial basement membrane at 1:20 titer

Studies to confirm the diagnosis of bullous pemphigoid and the blister level:

11/07 Direct immunofluorescence, left thigh (lesional skin): laminin-1 and type IV collagen stained on the dermal (floor) side of the bullae (using mouse monoclonal antibodies directed against human skin proteins). This indicates that the patient's blister is located above the lamina densa, likely in the mid or upper lamina lucida.

08/08 Enzyme-linked-immunosorbent serologic assay (ELISA) (serum collected 11/07): Both IgG and IgE autoantibodies were detected against type XVII collagen (also known as BP180 or BPAg2). However, only IgG autoantibodies were detected against BP230 (BPAg1).

Diagnosis:

Hemorrhagic bullae in bullous pemhigoid

Discussion:

Bullous pemphigoid (BP) is caused by immunoglobulin (Ig) G class of antibodies (Abs) targeting the upper dermal-epidermal junction protein type XVII collagen. It is the most common autoimmune blistering disease, primarily affecting the elderly. Hemorrhagic bullae are not frequently observed in patients with BP. In contrast, epidermolysis bullosa acquisita (EBA), caused by IgG Abs targeting the lower dermal-epidermal junction protein type VII collagen, is typically characterized by the presence of hemorrhagic bullae. The difference between BP and EBAs' clinical presentation, primarily the absence and presence of hemorrhagic bullae, could be explained based on the level of the skin location where the blister occurs. In EBA, the blister develops below the lamina densa, where dermal blood vessels are located, leading to the clinical observation of hemorrhagic bullae. The blister in BP occurs in the upper basement membrane zone of the skin, far above the lamina densa, therefore the dermal blood vessels are spared and hemorrhagic bullae are usually not observed.

There have been very few reports in the literature of hemorrhagic blisters, typically occurring in unusual blistering disorders exhibiting some features of BP, and in rare cases of dyshidrotic pemphigoid, a localized variant of BP. These reports lack extensive laboratory work-up to show the level at which the hemorrhagic blister occurred. We have done additional investigative studies to show that hemorrhagic blisters can occur above the lamina densa. Our patient's skin sample of a blister containing numerous red blood cells was stained for laminin 1 (a lower lamina lucida protein) and collagen IV (a lamina densa protein) to show that the blister occurred above the lamina densa.

In summary, we report a case of hemorrhagic blisters occurring above the lamina densa at the level of the mid to upper lamina lucida in a patient with generalized BP. We present this case as an unusual clinical presentation of BP. Interestingly, Enzyme-Linked ImmunoSorbent Assay of our patient's serum detected both IgG and IgE autoAbs against BP180. In review of the literature there is a reported correlation of IgE autoAb to BP180 with a severe variant of BP.

Essential Lessons:

- Hemorrhagic bullae, frequently observed in EBA, are rarely observed in BP.
- The mechanism by which hemorrhagic bullae occur in BP remains to be understood.

References:

1. Forschner A, Fierlbeck G. Localized pemphigoid on the soles of both feet. *Int J Dermato* 2005; 44:312-4.
2. Duhra P, Ryatt KS. Hemorrhagic pompholyx in bullous pemphigoid. *Clin Exp Dermatol* 1988; 13:342-3.
3. Kraigher O, et al**.** A mixed immunoblistering disorder exhibiting features of bullous pemphigoid and pemphigus foliaceus associated with Spirulina algae intake**.** *Int J Dermatol* 2008; 47: 61-63.
4. Zeynep Demirçay et al**.** Lichen planus pemphigoides: report of two cases. *Int J Dermatol* 2001; 40: 757-9.
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Case # 11

Case Presented by Amber Stevenson, MD
and Iris Aronson, MD

History of Present Illness:
This 71 year old male presented with a 2 year history of a persistent and progressive pruritic eruption. Lesions started on his thighs and quickly spread to his entire legs and then to arms, back and chest. The pruritus is somewhat improved with hydroxyzine and triamcinolone 0.1% ointment.

Past Medical History and Surgical History:
Eczema, arthritis, hypertension, history of methicillin-resistant skin infection 2007, chondrosarcoma (grade I, surgical removal from left chest wall in August 2005), and cataract surgery in June 2008

Medications:
Warfarin, furosemide, fosinopril, potassium chloride, tramadol, propoxyphene N-acetaminophen, memantine, donepezil, vitamin E, glucosamine chondroitin, hydroxyzine, and triamcinolone 0.1% ointment

Allergies:
Penicillin

Family History:
The patient's brother died of a myocardial infarction and his parents died from unknown causes at approximately 70 years of age

Social History:
The patient is currently retired and previously worked in maintenance. The patient grew up in southern Illinois and Arkansas where he spent a large amount of time in the sun.

Review of systems:
The patient reports severe pruritus, occasional shortness of breath, increased fatigue, and an unintentional 40 pound weight loss. He denies any fevers, chills, night sweats, abdominal pain, or joint pains.

Physical Examination:
The patient has numerous erythematous small annular papules with bright active borders and mild scale, many coalescing into larger reticulate plaques. These are diffusely distributed over his chest, abdomen, arms and legs with sparing of the face. His left chest wall has a large protruding soft mass without overlying ribs.

Histopathology:
01/08, 12/07 Left mid-leg, Left upper leg: Biopsies show atrophic epidermis with columns of parakeratosis forming cornoid lamellae. Underneath the lamella there is diminution of the granular layer. Superficial perivascular and dermal infiltrate of lymphocytes is also present.

Diagnosis:
Disseminated superficial actinic porokeratosis

Treatment and Course:
The patient was started on cetirizine for pruritus, and continued on hydroxyzine and topical triamcinolone 0.1% ointment. He was encouraged to follow-up with his primary care physician to look for recurrence of his prior chondrosarcoma or a new underlying malignancy, due to extensive skin involvement and

severity of pruritus and inflammation. His additional work-up has been negative to date and he has had slightly increased symptomatic improvement after starting topical betamethasone ointment.

Discussion:

Disseminated superficial actinic porokeratosis (DSAP) is the most common form of porokeratosis. It presents more frequently in women and Caucasians, rarely occurring in African Americans. Patients usually present in the third or fourth decades with small asymptomatic or mildly pruritic papules that have peripheral expansion, developing atrophic centers. DSAP papules tend to present in sun-exposed areas including the lower legs, while non-actinic papules may affect all areas. The face is rarely involved. There are several proposed mechanisms for this entity. One hypothesis proposes that the underlying process is a disorder of keratinization, where patients who are genetically susceptible to developing abnormal clones of keratinocytes show symptoms after exposure to a trigger such as ultraviolet (UV) light or immunosuppression. An additional proposed mechanism is that the dermal infiltrate is directed against an epidermal antigen, producing mediators that increase epidermal cell mitosis. In addition to the more common acquired form, there is also an autosomal dominant form with genetic heterogeneity. Studies have identified several gene loci although the exact mutations are still unknown.

Squamous cell carcinoma development has been reported in all variants of porokeratosis and is thought to be associated with p53 mutations induced by UV light, although, DSAP has the lowest risk of transformation. In addition to skin cancer, DSAP has also been associated with non-cutaneous malignancies including hematopoeitic malignancies and a few reported solid tumors. In patients with solid organ tumors it has been proposed that the DSAP occurred as a paraneoplastic phenomenon, with onset of disease correlating closely with malignancy diagnosis and improvement or even resolution of the skin findings after successful surgical and chemotherapeutic treatment. The solid organ tumors have included three cases of hepatitis C-related hepatocellular carcinoma, one case of cholangiocarcinoma, and one case of ovarian cancer. Each of these organ malignancies has a known association with p53 mutations.

Multiple therapies have been found to be effective for DSAP and individual porokeratosis lesions including cryotherapy, 5-fluorouracil, topical retinoids, and topical imiquimod. Newer studies have also shown good results with topical diclofenac sodium 3% gel. Laser therapy with Q-switched ruby and also CO2 lasers has been helpful. Oral retinoids may be a consideration for patients with widespread lesions and those that are less responsive to topical therapy.

Essential Lessons:

- p53 mutations are commonly found in porokeratosis lesions and may contribute to squamous cell carcinoma transformation and other concurrent malignancies.
- Topical immunomodulators are common successful treatment options for DSAP.

References:

1. Aranz-Salas I, Sanz-Treles A, Ojeda DB. P53 alterations in porokeratosis. *J Cutan Pathol* 2003; 30(7):455-58.
2. Cannavo SP, Borgia F, Adamo B, Guarneri B. Simultaneous development and parallel course of disseminated superficial porokeratosis and ovarian cancer: coincidental association or true paraneoplastic syndrome? *J Am Acad Dermatol* 2008; 58:657-60.
3. Cockerell C, Larsen F. Benign Epidermal Tumors and Proliferations in Dermatology, Second Edition. Bolognia JL editor in chief. Spain: Elsevier Limited, 2008: 1668-71.
4. Gold M, Muellenhoff M, Elewski B. Diclofenac sodium 3% gel as a potential treatment for disseminated superficial actinic porokeratosis. *J Eur Acad Dermatol Venereol* 2008 Aug 13. (E-pub)
5. Lolis MS, Marmur ES. Treatment of disseminated superficial actinic porokeratosis with Q-switched Ruby laser. *J Cosmet Laser Ther* 2008; 10(2):124-7.

Case # 12

Case Presented by Deborah Marble, MD
and Claudia Hernandez, MD

History of Present Illness:
This 35 year old female presented with a chief complaint of painful skin on her neck. She first noted skin changes in both axillae around age seven. The skin was described as becoming more yellowish, indurated, and wrinkled in appearance. Although the cutaneous lesions initially involved only the axillae, they progressed and developed on the neck, umbilicus, upper chest, and inguinal areas as well. These changes occurred gradually over an 8 year period.

Past Medical and Surgical History:
Cholecystectomy and ovarian cyst removal; gravida 3, para 3

Medications:
Pregabalin

Allergies:
No known drug allergies

Family History:
There is no history of pseudoxanthoma elasticum.

Social History:
The patient smokes a few cigarettes per day.

Review of systems:
She complained of leg pain, shortness of breath, chest pain, and menorrhagia while taking ibuprofen.

Physical Examination:
Physical examination was significant for white-to-yellow, indurated papules coalescing into large plaques on the lateral neck. Axillae, inguinal creases, nuchal and umbilical skin also had numerous yellow papules. Nuchal skin was thickened with a peau d'orange appearance while the axillae had numerous hanging folds of redundant skin.

Laboratory Data:
The following were positive or abnormal:
Triglycerides 162 mg/dl (45-150), lipase 15 u/l (22-51), and partial thromboplastin time 25.1 seconds (27.5-41).

The following were negative or within normal limits:
Complete blood count, complete metabolic panel, low density lipoprotein, high density lipoprotein, cholesterol, thyroid stimulating hormone, C-reactive protein, and amylase.

Diagnostic Procedures and Tests:
04/00 Cardiac catheterization: negative for coronary artery disease
04/08 Venous Doppler, lower extremities: normal.
06/08 Echocardiogram: Right ventricular cardiomyopathy
07/08 Ophthalmologic examination: Peau d'orange changes as well as angioid streaks in both eyes with the right eye streak extending under the fovea. No retinal neovascularization was found.

Histopathology:

06/08 Right axilla and nuchae: Biopsy shows short, curled, frayed, basophilic elastic fibers in the dermis. Overlying epidermis is unremarkable. Elastic fibers are highlighted by the elastic stain.

Diagnosis:
Pseudoxanthoma elasticum

Treatment and Course:
The patient considered phosphate binder therapy but pursued a more conservative option of daily tocopherol acetate and ascorbic acid therapy based on the regression of skin papules in a single anecdotal case report. Atenolol 25mg per day was initiated by her primary care physician with improvement of her chest discomfort. Smoking cessation was strongly recommended as well as avoiding aspirin and nonsteroidal anti-inflammatory drugs which inhibit coagulation. Surgical excision of selected affected skin was discussed, however she declined. Since presentation she has developed recurrent abdominal pain and is scheduled for an endoscopy.

Discussion:
Pseudoxanthoma elasticum (PXE) is an inherited multisystem disorder of connective tissue affecting the skin, blood vessels, and retina. It is caused by mutations in the adenosine triphospate (ATP)-binding cassette transporter C6 (ABCC6) gene, which encodes the multidrug resistance–associated protein 6 (MRP6). Theoretically, aberrations in this gene result in accumulation of various substances on elastic fibers with subsequent clumping of fibers. These irregular fibers then stimulate the deposition of calcium and other minerals resulting in the characteristic clinical presentation. Aberrant calcification of fragmented, degenerated elastic fibers in the mid-dermis as well as within the elastic tissue of small and mid-sized arteries are its cardinal histologic features. Patients present with varying degrees of yellowish papules coalescing into plaques. Most commonly the neck is affected, but other flexural areas can be involved and skin may become redundant. PXE may occur without skin findings due to variable penetrance leading to considerable variability in its presentation even within the same family.

The cutaneous effects of PXE are generally a cosmetic problem and no standardized treatment is available. Tocopherol acetate and ascorbic acid were found to be effective in clearing lesions in a single pediatric case possibly due to their antioxidant effects. Ocular changes occur in the majority of PXE patients starting with retinal mottled hyperpigmentation (peau d'orange), and progressing to angioid streaks, peripapillary atrophy, and retinal neovascularization. One of the most serious complications in PXE is accelerated atherosclerosis, while the most common cardiovascular symptom is intermittent claudication usually beginning in the third decade. Angina, hypertension, mitral valve prolapse, fibrous thickening of the atrioventricular valves and endocardium, diminished pulses, restrictive cardiomyopathy, and sudden death may also occur. Less frequent findings include calcification of the renal arteries leading to renovascular hypertension, as well as, hematemesis and melena due to gastrointestinal hemorrhages from elastic fiber calcification in gastric mucosal arteries. Aspirin is contraindicated in patient with PXE due to risk of fatal gastrointestinal hemorrhages

Essential Lesson:
- Pseudoxanthoma elasticum is a multisystem disease with associated morbidity and mortality.

References:

1. Plomp A, et al. ABCC6 mutations in pseudoxanthoma elasticum: an update including eight novel ones. *Molecular Vision* 2007; 14:118-124.
2. Qiujie J, et al. Pseudoxanthoma Elasticum Is a Metabolic Disease. *Journal of Investigative Dermatology* 2008 (advanced publication); 1-6.
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4. Takata T, et al. Treatment of pseudoxanthoma elasticum with tocopherol acetate and ascorbic acid. *Pediatric Dermatology* 2007; 24(4): 424-441.

Case # 13

Case Presented by Platina E. Coy Gershtenson, MD and Milena Lyon, MD

History of Present Illness:
This 61 year old female presented with a four month history of lesions on her right hand and arm. The eruption started on the right third finger a few days after cutting herself on broken glass while washing dishes. She noted a painful, red lesion with clear draining fluid accompanied by swelling of the digit. She was treated with empiric antibiotics with no improvement. Within a few weeks, the patient developed several firm, red tender lesions on her right arm which progressed proximally in a linear fashion. The patient has a fresh water fish tank in her home. She denies recent travel or gardening.

Past Medical History:
Coronary artery disease, diabetes mellitus, hypertension, and hyperlipidemia

Medications:
Lovastatin, glipizide, aspirin, amlodipine, enalapril, atenolol, and metformin

Allergies:
No known drug allergies

Family History:
No history of diabetes mellitus or recurrent infections.

Review of systems:
The patient denies fevers, chills, nausea, night sweats, malaise, anorexia, or joint pains.

Physical Examination:
The patient has an erythematous 0.5 cm nodule on the dorsal aspect of her third right finger and six erythematous firm slightly scaly nodules ranging in size from 0.5 cm to 1.5 cm on the right arm progressing proximally in a linear pattern. There is a palpable lymph node in the right axilla.

Laboratory Data:
The following laboratory studies were abnormal or positive:
Lesional tissue cultures grew *Mycobacterium marinum* resistant to isoniazid and doxycycline.

The following laboratory studies were normal or negative:
Complete metabolic panel and aerobic, anaerobic, and fungal tissue cultures.

Diagnostic Procedures and Tests:
03/08: Magnetic resonance imaging, right hand: Extensive soft tissue cellulitis of the first and third digits and dorsum of the hand extending into the thenar muscles and soft tissues. Abnormal fluid is present around the extensor and flexor carpi radialis tendons. There is no evidence of osteomyelitis.

Histopathology:
01/08: Right Arm: Biopsy shows a superficial and deep, mixed inflammatory cell infiltrate with poorly formed granulomas consisting of neutrophils intermixed with histiocytes. There is also significant vasculopathy and dermal edema. The epidermis is intact. The PAS and AFB stains are negative. Correlation with culture result is recommended based on histological findings.

Diagnosis:
Mycobacterium marinum cutaneous infection.

Treatment and Course:
Infectious disease was consulted regarding treatment. Pending identification of mycobacterium species, monotherapy was initiated with azithromycin 500 mg daily. Due to slow improvement, a six month course of triple antibiotic therapy was started consisting of azithromycin 500 mg daily, rifampin 600 mg daily, and ethambutol 1,200 mg daily. Throughout the course of therapy, daily warm compresses were locally applied. The patient improved with resolution of the lesions and the lymphadenopathy.

Discussion:
Nontuberculous mycobacteria (NTM) are slender, non-motile, acid-fast bacilli found worldwide. The most common species in the United States and Europe are *M marinum, M abscessus, M fortunitum,* and *M chelonae. M ulcerans* is endemic in Africa, West Pacific, Asia, and South America. While almost all NTM species can cause cutaneous disease, the most common culprits are *M marinum* and *M ulcerans*.

M marinum is acquired through contact with contaminated fresh or salt water and often results in cutaneous infections in both immunocompetent and immunocompromised patients. *M marinum* infection was first described as "swimming pool granuloma" after large outbreaks occurred in association with swimming pools. Subsequent to the practice of chlorination, most cases have been reported in fishermen and aquarium owners resulting in the term "fish tank granuloma." Common hosts include the fish *Betta splendens* and *Channa striata.* Infection from swimming pools has resurfaced due to improper chlorination and chlorine-resistant organisms. The portal of entry for *M marinum* is through open wounds typically on the upper extremity. This results in a tender erythematous draining nodule that can evolve into a verrucous nodule or crusted ulcer with an underlying abscess. The typical incubation period is 2 to 4 weeks, but can be as long as 9 months. The infection spreads proximally along lymphatics in a sporotrichoid pattern with development of multiple nodules. If left untreated, patients can develop tenosynovitis, septic arthritis and osteomyelitis, as well as disseminated disease in immunocompromised hosts.

Diagnosis of *M marinum* is challenging. Histological findings range from acute and chronic inflammation to ill-defined suppurative granulomas. The organisms are usually not seen on hematoxylin and eosin staining, but may be positive with acid-fast stains such as Ziehl-Neelson or Fite. Cultures grown at 30˚C to 33˚C are positive in only 75% and take 2 to 4 weeks to grow. Polymerase chain reaction can be used to confirm the diagnosis in culture negative cases.

Single lesions may resolve spontaneously, but can take up to 3 years. First line monotherapy includes minocycline, clarithromycin, or trimethoprim-sulfamethoxazole. In treatment resistant strains, ethambutol hydrochloride, and rifampin are added. Antibiotic sensitivities are difficult to determine because the organism responds differently *in vivo* than *in vitro.* Refractory cases may require surgical debridement.

Essential Lessons:
- *Mycobacterium marinum* causes a cutaneous infection that mimics sporotrichosis.
- In treatment resistant cases, triple therapy is often required for resolution of infection.

References:

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2. Fabroni C, Buggiani G, Lotti T. Therapy of environmental mycobacterial infections. *Dermatol Ther* 2008; 21(3):162-6.
3. Johnson RP, Xia Y, Cho S, et al. Mycobacterium marinum infection: a case report and review of the literature. *Cutis* 2007; 79(1):33-6.
4. Pandian TK, Deziel PJ, Otley CC, et al. Mycobacterium marinum infections in transplant recipients: case report and review of the literature. *Transpl Infect Dis* 2008; 10(5):358-63.

Case # 14

Case Presented by Caroline Schmitt, MD
and Lawrence Chan, MD

History of Present Illness:
This 67 year old man complained of a four year history of a nodule on his left third dorsal finger that arose after a penetrating dog bite six years prior to presentation. The nodule had grown, become tender, and occasionally drained clear fluid. The patient had been empirically treated with oral metronidazole and topical mupirocin for pyoderma for one month. After bacterial cultures had grown methicillin-resistant *Staphylococcus aureus*, the patient was given a ten-day course of oral tetracycline 500 mg twice daily which had led to subjective improvement. At two months follow-up, he complained of increased pain, tenderness, and blood-tinged yellowish drainage.

Past Medical History:
Psoriasis, psoriatic arthritis, actinic keratoses and Bowen's disease, coronary artery disease status-post stent placement, hypertension, chronic kidney disease, and asthma

Medications:
Methotrexate, prednisone, betamethasone lotion, calcipotriene cream, clobetasol ointment, carvedilol, clopidogrel, losartan, montelukast, folic acid, simvastatin, and oxybutyni.n

Allergies:
Penicillin, clindamycin, aspirin, and propoxyphene

Social History:
The patient is a Vietnam veteran and former tobacco smoker who denies recent travel.

Physical Examination:
On the dorsal proximal phalanx of the left third finger was a tender 2 cm pink scaly nodule with an apical superficial erosion with serosanguinous crust. There was no regional lymphadenopathy.

Laboratory Data/ Diagnostic Procedures and Tests:
None

Histopathology:
A shave biopsy from the left third finger shows a broad, asymmetrical, multinodular proliferation of nests of epithelial cells directly connected to the epidermis. A portion of the lesion has a more organoid growth pattern with proliferating basaloid cells, foci of clear cells, and cystic lumina, bearing resemblance to poroma. The remaining portion, particularly along the periphery and base, exhibit an infiltrative growth pattern marked by cytologic atypia, numerous mitoses, a few necrotic keratinocytes, and a dense lymphocytic infiltrate. Carcinoembryonic antigen stain highlights ductal structures and epithelial membrane antigen stain is diffusely positive.

Diagnosis:
Eccrine porocarcinoma

Treatment and Course:
The patient was referred to hand surgery for wide excision with intraoperative frozen sections and tissue rearrangement. He is receiving occupational therapy for postoperative weakness in the affected digit.

Discussion:

Eccrine porocarcinoma (EP) is a rare, potentially fatal neoplasm of acrosyringeal origin. About half of tumors develop from malignant transformation of a primary benign poroma; however, EP can occur as a primary tumor or can arise within other epithelial neoplasms. Only a few hundred cases have been reported worldwide. EP most commonly occurs on the legs and trunks of elderly individuals, rather than sites with high eccrine gland density as once thought. The clinical characteristics of EP are protean, with tumors resembling epidermal (e.g. squamous cell carcinoma or seborrheic keratosis) or melanocytic (e.g. amelanotic melanoma) neoplasms, pyogenic granulomata, or verrucae vulgaris. Histologically, there is an intraepidermal component of islands of basaloid cells with broad columns and nests of large cells extending deep into and anastomosing within the dermis. Pleomorphism, abortive ductal differentiation, high mitotic activity, necrosis, and clear cell change are common features. The majority of porocarcinomas stain positive for carcinoembryonic antigen and epithelial membrane antigen. Lymphovascular and perineural invasion are poor prognostic indicators. This case illustrates the impossibility of making an accurate clinical diagnosis without histological examination.

The average time from tumor onset to treatment is 4 years, suggesting a slow-growing nature. There is, however, an 11.7-17% recurrence rate after excision, a 9.6-19% rate of lymph node metastasis, and up to 11% rate of distant metastasis, suggesting that, although slow-growing, EP is a truly malignant neoplasm. Wide excision of the primary lesion is curative in about 80% of cases; Mohs micrographic surgery has been shown to be an effective and possibly preferable alternative. Because of the rarity of these tumors, specific guidelines for the investigation of possible disseminated disease in the absence of clinical signs (e.g. lymphadenopathy) have not been established. Further, the utility of sentinel lymph node biopsy has not been proven. For nodal disease, treatment is lymphadenectomy with chemotherapy. Radiotherapy is of limited benefit. The potential for local recurrence and metastasis requires long-term follow-up.

Immunosuppression may predispose to development of EP. Our patient was on methotrexate and prednisone for plaque psoriasis and psoriatic arthritis. Methotrexate is an S-phase-specific antimetabolite that impairs DNA synthesis through competitive inhibition of dihydrofolate reductase; it has been shown to impair both lymphocyte proliferation as well as migration of activated T cells into tissues. Lymphocyte dysfunction in patients with EP has elsewhere been demonstrated outside the context of methotrexate administration. In a report of five patients with EP of the head, one patient had multiple myeloma and another had chronic lymphocytic leukemia. Functional lymphocyte impairment was also evidenced in a patient with extensive metastatic clear cell EP in which dysfunction of interleukin 2 (IL-2) production and IL-2 receptor expression on peripheral blood lymphocytes was demonstrated. Finally, in another case report, two of five patients with EP were chronically immunosuppressed following renal transplantation. Whether immunosuppression leads to increased invasiveness or risk of recurrence remains to be seen.

Essential Lessons:

- Eccrine porocarcinoma (EP) is a rare malignant neoplasm arising from the acrosyringium.
- Because its clinical characteristics are nonspecific, biopsy of EP is essential for diagnosis.

References:

1. Gerber PA. Eccrine porocarcinoma of the head: an important differential diagnosis in the elderly patient. *Dermatology* 2008; 216(3): 229-33.
2. Lan CC, et al. Clear cell eccrine porocarcinoma with extensive cutaneous metastasis and peripheral lymphocyte dysfunction. *Br J Dermatol* 2003; 149(5): 1059-63.
3. Robson A. Eccrine porocarcinoma (Malignant Eccrine Poroma): A clinicopathologic study of 69 cases. *Am J Surg Pathol* 2001; 25(6): 710-20.
4. Wittenberg GP, et al. Eccrine porocarcinoma treated with Mohs micrographic surgery: a report of five cases. *Dermatol Surg* 1999; 25(11): 911-3.

Case # 15

Case Presented by Joanne Montgomery, MD
and Sophie Worobec, MD

History of Present Illness:
This 47 year old woman presented to her dermatologist with an itchy rash on her lateral neck which developed several weeks after using hydrocortisone 2.5% cream to treat hyperpigmented papules in the same area. The patient was not aware of reactions to jewelry or any other new products including soaps and perfumes. A potassium hydroxide preparation revealed yeast, and nystatin cream was added to the treatment regimen. After treating the area for 1 month with hydrocortisone and nystatin, the patient developed worsening redness, irritation and itching which progressed to involve the posterior neck. Both medications were discontinued and triamcinolone acetonide 0.1% ointment was started. One week later, the patient reported increased burning and itching as well as progression of the rash to include her antecubital fossae. She then presented to our Contact Dermatitis Clinic with a vesicular dermatitis of her neck. Triamcinolone was discontinued, betamethasone diproprionate 0.05% ointment twice daily was started, and patch testing was scheduled.

Past Medical History:
Allergic rhinitis, hypertension, uterine fibroids, and migraine headaches

Medications:
Hydrochlorothiazide, acetaminophen/aspirin/caffeine, ferrous sulfate, and diphenhydramine

Allergies:
No known drug allergies

Family History:
Sister with eczema

Review of systems:
The patient denied any fever, chills, night sweats, or weight changes.

Physical Examination:
The patient has confluent erythematous and vesicular plaques circumferentially around the base of the neck. There are well defined pink plaques with few linear excoriations over her bilateral antecubital fossae.

Laboratory Data/Diagnostic Procedures and Tests:
Patch testing with 47 standardized allergens of the North American Contact Dermatitis Series (Dormer Labs, Chemotechnique) plus 7 additional allergens including her hydrocortisone 2.5% cream, triamcinolone acetonide 0.1% ointment, and betamethasone diproprionate 0.05% ointment revealed the following reactions on day 4: 1+ to tixocortol-21-pivalate, 2+ to budesonide, 2+ to triamcinolone ointment, and 2+ to hydrocortisone cream.

Histopathology:
10/08: Neck: There is spongiotic dermatitis with superficial dermal perivascular infiltrate of lymphocytes, melanophages, and a few eosinophils. The overlying epidermis displays parakeratosis.

Diagnosis:
Allergic contact dermatitis with concomitant reactions to Group A and Group B corticosteroids

Treatment and Course:
The patient used betamethasone diproprionate ointment, a class C corticosteroid, to the affected areas and discontinued use of topicals containing her allergens. Her dermatitis completely resolved shortly thereafter.

Discussion:
Patch testing is the primary diagnostic tool for identifying allergens in allergic contact dermatitis. Different series of allergens are available varying from the Food and Drug Administration approved Thin-layer Rapid Use Epicutaneous Test (T.R.U.E. TEST®), to more extensive series, such as the North American Contact Dermatitis Group (NACDG) series which includes 65 allergens. The NACDG not only tests more allergens, but also includes different concentrations of allergens. This is done in an effort to establish recommendations for patch testing and create changes as new allergens are added and others are discarded (e.g. thimerosal).

Corticosteroids are common anti-inflammatory agents used in a variety of dermatologic conditions; however, they can also cause allergic contact dermatitis. The presence of chronic dermatitis, failure of an eruption to clear with topical corticosteroids and/or exacerbation with the use of corticosteroids should lead clinicians to consider patch testing.

Corticosteroids are broken into four structural classes. An allergy to one structural class does not necessarily indicate allergy to all corticosteroids within that class, although cross-reactivity is more likely. Cross-reactivity between the different structural groups is uncommon, however, concomitant reactions between groups have been reported. Tixocortol-21-pivalate is the marker used to test for allergy to corticosteroid structural class A, of which hydrocortisone is a member. Budesonide is the marker for structural class B, which includes triamcinolone acetonide, and of Group D2, which includes the labile prodrug esters. Both tixocortol and budesonide have been included in the NACDG series since 1995 and were recently added to the expanded T.R.U.E. TEST® series. A recent Mayo Clinic review reported the percent positive allergic reaction to tixocortol-21-pivalate as 3.0% and to budesonide as 1.5%, with corresponding values for a similar time period reported as 2.9% and 2.2%, respectively by the NACDG.

Our patient's clinical history correlated well with her patch test results and knowledge of these allergies proved to be important in her management.

Essential Lesson:
- Allergic contact dermatitis should be considered in patients with chronic dermatitis and in cases which are exacerbated by or fail to respond to topical corticosteroids.

References:

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2. Davis MD, Scalf LA, Yiannias JA, et al. Changing trends and allergens in the patch test standard series: a Mayo Clinic 5-year retrospective review, January 1, 2001 through December 31, 2005. *Arch Dermatol* 2008; 144(1):67 72.
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Case # 16

Case Presented by Rikk Lynn, MD, David Fretzin, MD and Iris Aronson, MD

History of Present Illness:
This 75 year old man presented with a five month history of blistering lesions involving his head, trunk, and mouth in November 2003. The biopsy was consistent with pemphigus vulgaris. He was initially started on mycophenalate mofetil and prednisone. Due to various complications, prednisone was tapered and intravenous immunoglobulin (IVIG) infusions were started as steroid sparing treatment. Despite this regimen, he continued to have worsening of his disease. Dapsone therapy was then added with little improvement at maximum doses. The patient did not wish to start cyclophosphamide secondary to potential malignancy side effects and he also had contraindications to azathioprine treatment. On November 2006 he stopped all immunosuppressive agents, except low dose prednisone, and began a rituximab and IVIG treatment protocol as outlined below. The patient achieved full remission and had been off all treatments for a period of just over one year until suffering a severe reactivation of his pemphigus in June 2008.

Past Medical History:
Cerebrovascular accident, diabetes mellitus, hypertension, hyperlipidemia, osteoporosis, glaucoma, and hypothyroidism

Medications:
Rituximab, IVIG, alendronate, glyburide/metformin, simvastatin, levothyroxine, metoprolol, losartin/hydrochlorothiazide, timolol ophthalmic, brimonidine, prednisone, nicotinamide, and doxycycline

Allergies:
No known drug allergies

Review of systems:
The patient describes mild fatigue and weakness, but denies any recent fevers, night sweats or chills

Physical Examination:
There are multiple vegetative, brown plaques overlying an erythematous scalp. The face, trunk, and upper extremities have scattered superficial erosions of varying size and in different stages of healing. Some erosions display a brown overlying crust.

Laboratory Data/Diagnostic Procedures and Test:
Indirect immunofluorescence :
11/03 1:160 - initial presentation on monkey esophagus
11/06 1:640 - severe flare, rituximab/IVIG therapy started
12/06 1:160 - completed 6 rituximab infusions and 2 plasmapheresis treatments
11/07 zero - patient in full remission
06/08 1:40 - severe reactivation after being in remission for 14 months

Histopathology:
04/05 The epidermis shows hyperkeratosis with scale-crust, acanthosis, and suprabasal separation. The acantholytic cells are seen within the intraepidermal vesicle. A dense lymphocytic infiltrate is observed in the perivascular area. Occasional neutrophils and nuclear dust are seen.

Diagnosis:
Pemphigus vulgaris recurrence after rituximab therapy

Treatment and Course:

In November 2006 the patient stopped all immunosuppressive agents except low dose prednisone and began rituximab infusions once weekly for three weeks followed by an IVIG infusion on the fourth week. The rituximab/IVIG month long cycle was repeated once and was followed by an additional once monthly infusion of rituximab and IVIG for four months (Ahmed October 26, 2006 protocol). The patient achieved full remission and had been off all pemphigus vulgaris treatments for a period of just over one year until suffering a reactivation of his pemphigus. He has since been treated with an additional cycle of rituximab once weekly for three weeks followed by IVIG on the fourth week. He has had significant improvement and is scheduled to undergo two more cycles of rituximab/IVIG once monthly. The patient is presented for clinical interest and discussion of new treatment options for patients with recalcitrant pemphigus vulgaris. The case also highlights reactivation of pemphigus after completing the rituximab/IVIG cycle and having a period of sustained remission.

Discussion:

Pemphigus describes a group of blistering skin diseases in which autoantibodies are directed against the cell surface of keratinocytes resulting in the loss of cell-cell adhesion.

In general, immunosuppressive agents such as prednisone, mycophenolate mofetil, azathioprine, and cyclophosphamide may result in control of the disease and an increased percentage of clinical remissions. High dose IVIG has been used as an additional therapy for resistant disease, though its mechanism of action has yet to be elucidated. Plasmapheresis is useful for quickly reducing the titers of circulating autoantibodies and should be considered for severe pemphigus vulgaris (PV).

Multiple studies have described a new treatment option for unresponsive PV with rituximab and IVIG therapy. One of the standard treatment courses used consists of rituximab infusions once weekly for 3 weeks and then IVIG on the fourth week. This cycle is repeated once more and then followed by monthly infusions of rituximab and IVIG for 4 additional months. In the Ahmad et al study, 9 of 11 patients had rapid resolution of their lesions and achieved clinical remission lasting 22 to 37 months. In this case, we present a patient that received the above rituximab/IVIG protocol and had sustained remission, off all treatments, for a period of over one year and then suffered reactivation of his pemphigus. We present this case to highlight that the rituximab/IVIG therapy is very effective in treatment resistant pemphigus cases, but is by no means a cure. Rituximab has been used more extensively in patients with B cell lymphomas and multiple studies to date have shown better outcomes for patients that, after remission, are continued on rituximab maintenance therapies every 3 to 6 months. More investigation is needed to determine whether patients treated with the above protocol for pemphigus will require maintenance therapy with rituximab after achieving remission.

Essential lessons:

- Rituximab/IVIG is a novel treatment for severe and recalcitrant cases of pemphigus vulgaris.
- Protocols have been developed for initial treatment phases but there is still a need for appropriate maintenance therapy guidelines as more patients develop reactivation of disease.

References:

1. Ahmed AR, et al. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; 355: 1772-1779.
2. Diaz LA, et al. Rituximab and pemphigus—a therapeutic advance. *N Engl J Med* 2007; 357: 605-607.
3. Cianchini G, et al. Treatment of severe pemphigus with rituximab. *Arch Dermatol* 2007; 143:1033-1038.
4. Barrera MV, Mendiola MV, Bosch RJ, Herrera E, et al. Prolonged treatment with rituximab in patients with refractory pemphigus vulgaris. *J Dermatolog Treat* 2007; 18(5):312-4.
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Case # 17

Case Presented by Sabrina Guillen, MD, Helen Chen, MD and Michelle Bain, MD

History of Present Illness:
This 9 year old Hispanic female presented with a one year history of an asymptomatic papule on her buccal mucosa that has since multiplied. There has been no evidence of regression. The patient's parents deny her ever having had any other areas of involvement or a previous history of verrucae.

Past Medical History:
Lichen striatus

Medications:
None

Allergies:
None

Family History:
No history of skin conditions, including verrucae or condylomata acuminata. Mother with no history of cervical dysplasia.

Review of systems:
The patient is otherwise healthy and denies fevers, chills, weight loss, fatigue, hoarseness, or stridor.

Physical Examination:
Over the retro-commissural and buccal mucosa are several pink, soft, sessile papules. The nasal sinuses, hands, and feet are clear.

Laboratory Data:
The following were negative or within normal limits:
Complete blood count with differential and human immunodeficiency virus antibody screen.

Diagnostic Procedures and Tests:
10/08 ThinPrep test, Buccal mucosa: Polymerase Chain Reaction amplification using consensus primers that detect all human papillomavirus DNA was positive. The assay specifically amplifying HPV types 6,11,16,18,31,33,35,39, and 45 was negative.

Histopathology:
06/08 Right buccal mucosa: Biopsy shows epidermal hyperplasia with pallor of the epidermal cells and some clubbing of the rete ridges. A few binucleated cells are identified. There is, however, no significant hypergranulosis or finger-like projections/papillomatosis.

Diagnosis:
Focal epithelial hyperplasia (Heck's disease)

Treatment and Course:
The patient has not had treatment to date. She is presented for discussion of diagnosis and treatment options.

Discussion:

Focal epithelial hyperplasia (FEH) is a rare, benign disease of the oral mucosa most commonly associated with human papillomavirus (HPV) 13 and 32. FEH affects various ethnic groups and races, but is most commonly seen in Central and South American Indians, as well as Greenland Eskimos. The condition primarily affects children but can occur in young and middle-aged adults. A higher incidence in close communities and among family members suggests an infectious pathogenesis. The occurrence of FEH in human immunodeficiency virus infected patients has also been reported, but typically multiple other HPV types are concomitantly present.

Common sites of involvement include the labial, buccal, and rarely lingual mucosae. FEH is characterized by multiple 1-5 mm, painless flat-topped or dome-shaped, pink to white papules, which may coalesce to form plaques.

The diagnosis of FEH can be made clinically, but histologic examination may show evidence of viral infection. Histologically, FEH is somewhat different from other HPV infections in that there is often significant acanthosis with minimal papillomatosis. The thickened mucosa extends upward, not down into underlying connective tissues, and the rete ridges are typically widened, sometimes club-shaped, as was evident in our patient.

The differential diagnosis includes squamous cell papilloma, the most common benign oral epithelial tumor, and condyloma acuminatum, which is typically acquired through oral sex, autoinoculation, or maternal transmission. Both these entities are associated with HPV 6 and 11, for which our patient was negative. Verruca vulgaris**,** or common wart, associated with HPV 2 and 4, is the most prevalent HPV lesion of the skin, but can also be found in the oral mucosa. In the oral cavity, verrucae typically involve mucosa in which keratinization closely resembles that of skin, such as the lip, hard palate, and gingiva.

Some authors do not advocate treatment in FEH as the lesions may undergo spontaneous regression, particularly in children. However, there have been cases where FEH persists well into adulthood. Nonetheless, therapeutic intervention may be indicated when lesions are functionally or aesthetically unacceptable. Common therapies for localized lesions include simple excision, cryosurgery, electrocautery, and curettage. Patients with more widespread involvement have been treated successfully with CO_2 laser, topical interferon β, and 5% imiquimod cream.

Essential Lesson:

- When viral-induced changes in the oral cavity are suspected, one should consider sending a portion of tissue for PCR amplification of HPV DNA. Certain HPV types are associated with a greater risk of malignancy, dictating more aggressive therapy.

References:

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2. Carlos R, Sedano HO. Multi focal papillomavirus epithelial hyperplasia. *Oral Surg Oral Med Oral Pathol* 1994; 77: 631–635.
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Case # 18

Case Presented by Tanya Bulj-Stevens, MD
and Iris Aronson, MD

History of Present Illness:
This 51 year old female presented with a 2 year history of an itchy remitting and recurring rash that began on her upper abdomen and underneath her breasts which subsequently progressed to her neck and right groin area. She complained of painful crusted erosions and fissures, which resolved leaving dark patches. The patient noted temporary improvement with topical steroid medications; however, the rash recurred within a few weeks after cessation. She denies any ulcers in the mouth.

Past Medical and Surgical History:
Migraines and fibroidectomy

Medications:
Acetaminophen/aspirin/caffeine and aspirin

Allergies:
No known drug allergies

Family History:
No skin conditions in the family

Physical Examination:
The patient has hyperpigmented patches and thin scaly plaques with scattered crusted and occasionally macerated erosions on her bilateral neck, chest, inframmamary area, upper abdomen, and right upper medial thigh.

Laboratory Data/Diagnostic Procedures and Tests:
The following were negative or within normal limits:
KOH of left axilla, tuberculosis quantiferon gold anti nuclear antibody, complete blood cell count, complete metabolic panel, Glucose-6-phosphate dehydrogenase, thiopurine methyltransferase

Histopathology and Immunopathology:
07/08 Skin, left axilla: The biopsy shows epidermal hyperplasia with suprabasal acantholysis and intercellular edema involving multiple layers of epidermis, leading to a "dilapidated brick wall" appearance. This is associated with increased orthokeratosis and parakeratosis. Areas of elongated papillae covered by one or several layers of keratinocytes are also identified. The dermis shows a superficial and mid-dermal perivascular infiltrate of mostly lymphocytes
07/08 Direct immunofluorescence, left axilla: There is a suprabasal cell split with acantholysis throughout the epidermis and negative staining. There was no deposition of conjugate anti-IgG, IgM, IgA, C3, or fibrin at the intercellular space, basement membrane zone, or blood vessels.
08/08 Indirect immunofluorescence: Negative on monkey esophagus substrate

Diagnosis:
Hailey-Hailey disease

Treatment and Course:
The patient is currently maintained on doxycycline 100mg twice daily, tacrolimus 0.1% ointment, betamethasone dipropionate ointment, and clindamycin 1% lotion.

Discussion:

Hailey-Hailey disease (HHD) is an autosomal dominant genodermatosis with abnormal cell-cell adhesion within the epidermis that usually develops during the second or third decade, but may be delayed until the fourth or fifth decade. It results in flaccid blisters that give rise to macerated or crusted erosions, with predilection for intertriginous areas. The cutaneous signs are known to be exacerbated by triggers such as heat, friction and perspiring; while UV irradiation does not appear to influence the course of disease. Colonization and secondary infections frequently complicate the course of disease. While the disease course is difficult to predict, life expectancy is not altered. Histologically, extensive acantholysis throughout the epidermis ("dilapidated brick wall") is seen and only rare dyskeratotic keratinocytes (in contrast to Darier's disease) may be observed. Grover's disease may be indistinguishable from HHD based on histological findings, but these two entities are readily distinguished on the basis of clinical features. Direct immunofluorescence is negative, thus excluding pemphigus vulgaris.

HHD is linked to mutations in the Golgi apparatus Ca^{2+} ATPase ATP2C1 (gene product hSPCA1), most likely through haploinsufficiency. ATP2C1 mutation results in inadequate filling of the Golgi apparatus calcium stores. hSPCA1 is an intracellular pump that sequesters calcium to the Golgi lumen. Dysfunction of this pump is thought to impair the normal processing of the proteins necessary for efficient cell-to-cell adhesion, resulting primarily in acantholysis in the stratum spinosum.

The mode of inheritance is autosomal dominant with complete penetrance, but the age of onset and expressivity varies greatly among the affected members of a family. To date, over 90 pathological mutations scattered throughout ATP2C1 have been described with no indication of mutational hotspots or clustering of mutations. Incidence of new sporadic mutations is low but may be even lower as clinically unnoticed very mild forms of the disease have been observed. Our patient reported no family history, which could be explained by either new somatic mutation or the possibility that other family members carrying the same mutated ATP2C1 gene have clinically unnoticed mild forms of the disease. There is no evidence to date of a correlation between the phenotype and the underlying ATP2C1 mutations. Direct nucleotide sequencing of the ATP2C1 gene in all patients and reverse transcription polymerase chain reaction analysis, using RNA extracted from skin biopsy, may help expand the known mutation spectrum in HHD and understand the genotype-phenotype correlations more precisely.

Treatment of HHD mainly relies on general measures of avoiding friction and sweating as well as topical therapy. Topical corticosteroids are an effective treatment in many patients, and are often combined with topical antimicrobials and cleansers to prevent secondary infections. With the exception of antimicrobial agents, there is no strong evidence to support the use of any particular systemic therapy. The use of immunosuppressive drugs, e.g. prednisone, cyclosporine, methotrexate, dapsone, and most recently alefacept and entanercept in severely affected individuals is limited to case reports.

Essential Lessons:

- Hailey-Hailey disease is linked to mutations in the Golgi apparatus Ca^{2+} ATPase ATP2C1.
- The mode of inheritance is autosomal dominant with complete penetrance but greatly variable expressivity.

References:

1. Hurd DS, Johnston C and Bevins A. A case report of Hailey-Hailey disease treated with alefacept (Amevive). *Br J Dermatol* 2008; 158(2):399-401.
2. Zhang F, Yan X, Jiang D et al. Eight novel mutations of ATP2C1 identified in 17 Chinese families with Hailey-Hailey disease. *Dermatology* 2007; 215(4):277-83.
3. Hamada T, Fukuda S, Sakaguchi S et al. Molecular and clinical characterization in Japanese and Korean patients with Hailey-Hailey disease: six new mutations in the ATP2C1 gene. *J Dermatol Sci* 2008; 51(1):31-6.
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Case # 19

Case Presented by Joanne Montgomery, MD
and Lawrence Chan, MD

History of Present Illness:
This 62 year old African American male presented with a two week history of pustular lesions, which started on the tip of his nose and spread to the right nasal ala. In the two weeks following presentation, the lesions progressed to involve the majority of his nose. The patient also had a one month history of hemoptysis and cough, which was being treated as pneumonia with a course of amoxicillin/clavulanate and azithromycin. Treatment with the above antibiotics did not improve the pustular skin eruption or his lung symptoms.

Past Medical History:
Hypertension, benign prostatic hypertrophy, and a stroke in 1992 complicated by seizure disorder

Medications:
Aspirin, atenolol, finasteride, and terazosin

Allergies:
No known drug allergies

Social History:
The patient lives alone and has no pets. He denies any travel outside of the Chicago area in the past 3 to 4 years. He smoked one half pack of cigarettes per day for 30 years, but quit in 2004.

Review of systems:
The patient reports recent cough and hemoptysis. He denied fever, chills, shortness of breath, myalgias, arthralgias, and weight changes.

Physical Examination:
Over the tip of the nose extending onto the right more than the left nasal alae were multiple heaped up pink to gray-brown papules intermixed with a few pustules and areas of overlying honey-colored crust. Submental and anterior cervical lymphadenopathy was present. The patient was afebrile.

Laboratory Data:
The following were positive or abnormal:
Histoplasma urinary antigen <0.6 ng/mL (<0.6-3.9 is low positive)

Diagnostic Procedures and Tests:
11/07 Tissue culture, nose: few colonies of *Candida albicans*, one colony of *Penicillium species*
10/07 Computed tomography, chest: There is a large pleural based soft tissue density in the left lower lobe posterolaterally measuring approximately 7.3cm. There are two smaller densities in the left lower lung and one at the right base. There are bilateral basilar interstitial changes consistent with scarring or atelectasis. There is no large mediastinal or hilar adenopathy.
5/08 Computed tomography, chest: There is resolution of the patchy consolidations in the posterior aspect of the left lower lobe compared to previous scans since 10/07. Minimal residual pleural thickening with few linear interstitial densities at the posterior aspect of the left lower lobe remain, consistent with minimal residual inflammatory process or atelectasis.

Histopathology:

11/07 Nose: There is marked pseudoepitheliomatous epidermal hyperplasia with a suppurative and granulomatous inflammatory infiltrate. Also visualized are multinucleated giant cells with fungal yeast identified focally. The fungal yeast with thick-walled capsule measuring approximately 10-15μm is highlighted by the Grocott's Methenamine Silver stain.

Diagnosis:

Blastomycosis

Treatment and Course:

The patient was placed on itraconazole 200mg twice daily for a planned duration of 6-9 months. The skin lesions and lung symptoms improved almost completely within 2-3 weeks of therapy. The left lung lesion seen on initial computed tomography (CT) in October 2007 had also almost completely resolved on repeat CT 6 months after initiation of therapy. The patient completed a total of 7 months of itraconazole.

Discussion:

Blastomycosis is endemic to the southeastern and south central United States, in the Great Lakes region, as well as locations near the Missouri, Mississippi and Ohio Rivers. Infection is most often caused by inhaling conidia of the dimorphic fungus *Blastomyces dermatitidis*. Cutaneous blastomycosis can be either primary, through direct inoculation after trauma to the skin, or secondary, from lymphatic or hematogenous spread from a distant site, mostly commonly the lungs. Acute primary pulmonary infection can be asymptomatic or present with symptoms similar to atypical pneumonia. Incubation period ranges from 3 weeks to 3 months. Patients are commonly misdiagnosed and treated for bacterial pneumonia with antibiotics without improvement.

Cutaneous blastomycosis typically presents as either verrucous or ulcerative skin lesions. Verrucous lesions are most commonly seen on areas of exposed skin such as extremities and face and are characterized by serpiginous, advancing, raised borders with atrophic centers. Ulcerative skin lesions often begin as a small pustule, which progresses to an ulcer with heaped borders and an exudative base.

Diagnosis of blastomycosis is often a challenge. Ideally diagnosis is made by microscopic visualization or culture of the organism from infected tissue or sputum. Yeast forms can be seen on hematoxylin and eosin-stained sections, but are more easily visualized with Grocott's methenamine silver (GMS) stain or periodic acid-Schiff (PAS) stain. Multiple sections should be examined and repeat biopsy may be necessary.

In general, patients with blastomycosis infection require systemic anti-fungal therapy. Amphoteracin B is the treatment of choice for patient with life-threatening or central nervous system infection. In contrast, azole antifungals, in particular itraconazole, are less toxic and are the preferred treatment for immunocompetent patients with mild pulmonary or extrapulmonary disease.

Essential Lessons:

- Blastomycosis can account for acute and chronic papulopustular skin eruptions, especially in endemic areas such as Chicago.

References:

1. Garvey K, Hinshaw M, Vanness E. Chronic disseminated cutaneous blastomycosis in an 11 year old, with a brief review of the literature. *Pediatr Dermatol* 2006; 23(6):541-545.
2. Mason AR, Cores GY, Cook J, et al. Cutaneous blastomycosis: a diagnostic challenge. *Int J Dermatol* 2008; 47(8):824-30.
3. Chapman SW, Bradsher Jr RW, Campbell Jr GD. Practice guidelines for the management of patients with blastomycosis. *Clin Infect Dis* 2000; 30:679-683.

Case # 20

Case Presented by Jonathan Pewitt, MD
and Iris Aronson, MD

History of Present Illness:
This 45 year old male presented to dermatology three years ago as a consult from his ophthalmologist**,** Elmer Tu, MD, after direct immunoflourescence of a right conjunctival biopsy was consistent with cicatricial pemphigoid. Prior to his presentation he described a two year history of redness, irritation and ingrown eyelashes of the right eye with recurrent corneal infections and chalazia. Plastic surgery had performed incision and drainage of a chalazion involving the right eye in the past.

Past Medical History:
Benign paroxysmal positional vertigo, hypertension, hyperlipidemia, and diverticulosis

Medications:
Doxycycline, dapsone, mycophenolate mofetil, amlodipine-atorvastatin, alprazolam, aspirin, ocular lubricant, loteprednol ophthalmic suspension, and prednisolone ophthalmic suspension

Allergies:
Tetanus toxoid

Family History:
Maternal grandfather deceased from bladder cancer and his brother has celiac disease and type 1 diabetes

Social History:
The patient occasionally consumes alcohol and works as an accountant and teacher.

Review of systems:
The patient reports lethargy and continued pain and burning of the right eye. He denies any fever, chills, nausea, vomiting, change in bowel habits, weight loss, mouth sores, or skin involvement.

Physical Exam:
The patient has bilateral conjunctival injection with the right eye more involved than the left. The eyelids are minimally edematous with entropion and dilated vasculature of both upper eyelids. There is a large symblepharon in the lateral fornix of the right eye.

Laboratory Data:
The following were positive or abnormal:
Thiopurine methyltransferase 28.5 U/mL (15.1-26.4), hemoglobin 12.3 g/dL (13.2-18.0), and hematocrit 36.9% (38.0-55.0).

The following were negative or within normal limits:
Total IgM, IgG, IgA levels, complete blood count, complete metabolic panel, thyroid stimulating hormone, glucose-6-phosphate dehydrogenase, tissue transglutaminase IgG and IgA, erythrocyte sedimentation rate, serum protein electrophoresis, and urinalysis

Histopathology and Immunopathology:
11/05 H&E, right eye conjunctiva: There is subtle sub-epithelial clefting with mixed inflammatory cell infiltrate in the lamina propria and slightly increased fibrosis.
11/05 Direct immunoflourescence, right eye conjunctiva: There is positive staining of the basement membrane zone; focal linear for C3, linear for IgM, and extensive thick linear for fibrin.

10/07, 05/08 Indirect immunoflourescence: On saline split skin for IgM. There are multiple focal areas of fine linear staining at the basement membrane zone. There is positive staining for ANA of the epidermal cell nuclei. Staining for IgA and IgG is negative.

Diagnosis:
IgM Cicatricial pemphigoid

Treatment and Course:
The patient has been on doxycycline, dapsone, and mycophenolate mofetil. He has also used intermittent courses of prednisolone eye drops and loteprednol eye drops for disease flairs. He has had multiple epilations of offending eyelid cilia. Progression of disease has been stable on mycophenolate mofetil.

Discussion:
Cicatricial pemphigoid (CP) is an autoimmune blistering disorder that involves predominantly the mucosae. Ocular CP starts as a non-specific conjunctivitis with erythema, pain, and foreign body sensation. It progresses through chronic inflammation to scar tissue formation leading to fibrous adhesions between the bulbar and palpebral conjunctivae. It can also lead to abnormal growth of the eyelashes from the orifices of the meibomian glands and misdirection towards the globe. Diagnosis is based on direct immunoflourescence (IF) microscopic examination with IgG, IgA, IgM, complement and fibrin. Disease activity is monitored with indirect IF and ophthalmologic examination.

CP is associated with autoantibody production to one or more components of the basement membrane zone. Antibodies to beta-4 integrin have been associated with ocular CP and antibody titers correlate with disease activity. Autoantibodies to alpha-6 integrin are implicated in oral CP. Other identified antigens include bullous pemphigoid (BP) 230, laminin 332 and BP 180 including several of its ectodomains. Oyama et al. demonstrated an association between disease severity and autoantibodies to multiple BP 180 antigens, although not to BP 230 or Beta-4 integrin. Autoantibody reactivity was further associated with certain Human Leukocyte Antigen (HLA) class two alleles.

The persistence of IgM in this patient is unexplained. This patient has no immunoglobulin deficiency or IgM gammopathy to explain this failure to class switch. Immunoglobulin class switching from IgM to IgG or IgA is a T cell dependent process that involves an interaction between a type two helper T cell and the IgM producing antigen specific B cell. T cell independent antibody production can occur with certain antigens such as polysaccharides, glycolipids and nucleic acids. This can result in IgM production with low affinity and limited class switching. A polysaccharide moiety of a conjunctival basement membrane glycoprotein acting as an antigen could result in IgM persistence.

Essential Lessons:
- Cicatricial pemphigoid typically involves IgG or IgA autoantibodies to basement membrane antigens.
- Autoantibody titers, measured with indirect immunoflourescence, correlate with disease activity.

References:

1. Kanitakis J. Indirect immunofluorescence microscopy for the serological diagnosis of autoimmune blistering skin diseases a review. *Clin Dermatol* 2001; 19(5):614-21.
2. Letko E, Gürcan HM, Papaliodis GN, et al. Relative risk for cancer in mucous membrane pemphigoid associated with antibodies to the beta4 integrin subunit. *Clin Exp Dermatol* 2007; 32(6):637-41.
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