Chicago Dermatological Society

December 2010
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, December 8, 2010

David Fretzin Lecture

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

Program

Conference Locations

Student Center West (SCW) – 828 S. Wolcott, 2nd Floor
Dermatology Clinic, 1801 W. Taylor St., Suite 3E

8:00 a.m.	Registration Opens for All Attendees *Student Center West, 2nd floor*
9:00 a.m. - 10:00 a.m.	**Resident Lecture** – *SCW Chicago Room A-C* "Retinoid Pharmacology in Human Skin In Vivo" *Sewon Kang, MD*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** Patient Viewing *Dermatology Clinic, Suite 3E* Slide Viewing *Student Center West, Room 206 A/B*
11:00 a.m. - 12:15 p.m.	**General Session** - *SCW Chicago Room A-C* FRETZIN LECTURE: "Natural Skin Aging and Its Antagonism With Retinoid" *Sewon Kang, MD*
12:15 p.m. - 12:45 p.m.	Box Lunches & visit with exhibitors *SCW - 2nd Floor Foyer*
12:45 p.m. - 1:00 p.m.	**CDS Business meeting** – *SCW Chicago Room A-C*
1:00 p.m. - 2:30 p.m.	**Case Discussions** – *SCW Chicago Room A-C*
2:30 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS monthly meeting – Wednesday, March 2, 2011 at Stroger Hospital of Cook County; Timothy G. Berger, MD from the University of California-San Francisco

CDS coding seminar – Saturday, January 22, 2011 for members & staff. Registration materials will be in the mail shortly.

Please note the following date change . . .
The May monthly meeting sponsored by Rush University is now on Wednesday, May 11 at the Stephens Convention Center in Rosemont.

Watch for details on the CDS website: www.ChicagoDerm.org

Guest Speaker

SEWON KANG, MD

Noxell Professor & Chairman
Department of Dermatology
Johns Hopkins School of Medicine

Delivering the David Fretzin Lecture

Since 2008, Dr. Kang has served as the chairman of the Department of Dermatology and is dermatologist-in-chief at Johns Hopkins Hospital. He earned his medical degree at the University of Michigan Medical school in 1987 and also earned an M.P.H. at the University of Michigan School of Public Health in 1982. Dr. Kang completed a residency in dermatology at Harvard Medical School, Massachusetts General Hospital in 1992 and was chief resident in 1991. He engaged in a research fellowship (1989-90), also at Harvard. Dr. Kang has a connection to the Chicago area having graduated from Glenbrook North High School. He has received numerous honors and awards and has a long list of research grants.

CME Financial Disclosure: Dr. Kang has disclosed the following financial relationships: grant/research support - Galderma; intellectual property - co-inventor of IP owned by the University of Michigan.

Continuing Education Credit

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Conference"

December 8, 2010 *Chicago, Illinois*

Participants must attend entire session to receive all types of credit. CFMC hosts an online evaluation system, certificate and outcomes measurement process. Following the conference, you must link to CFMC's online site (link below) to complete an evaluation form, in order to receive your continuing education statement of hours (certificate). Once the evaluation form is complete, you will automatically be sent a copy of your certificate via email.

Continuing Education evaluation and request for certificates will be accepted up to 60 days post activity date. The Colorado Foundation of Medical Care (CFMC) will keep a record of attendance on file for 6 years. CFMC contact information: 303-695-3300, ext. 3139.

Link address to evaluation form:
http://www.yourcesource.com/eval/?act=468!12082010

JOINT SPONSOR STATEMENT

This Continuing Educational activity is Joint-sponsored by the **Colorado Foundation for Medical Care, Office of Continuing Education** and the **Chicago Dermatological Society**. **CFMC is accredited by the ACCME to provide continuing medical education for physicians.**

GOAL / PURPOSE

To broaden the clinical knowledge of dermatologists with respect to diagnostic.

SESSION OBJECTIVES

Upon completion of sessions, participants will be able to apply new knowledge and skills in the area of physician learning.

After participating in this program, physicians should be able to:

1. Explain the processes involved in the natural aging of skin.
2. Describe the impact of retinoid with respect to the processes of naturally aged skin.
3. Discuss how knowledge of retinoid antagonism in natural skin aging can be incorporated successfully in the typical dermatology practice.

CREDIT STATEMENTS

CME CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through joint sponsorship of the Colorado Foundation for Medical Care, Office of Continuing Education (CFMC OCE) and Chicago Dermatological Society. CFMC is accredited by the ACCME to provide continuing medical education for physicians.

Colorado Foundation for Medical Care designates this educational activity for a maximum of **5 *AMA PRA Category 1 Credits™*.** Physicians should only claim credit commensurate with the extent of their participation in the activity.

CFMC has no financial responsibility for this activity.

DISCLOSURE STATEMENTS

The following faculty member has disclosed that they have the following financial relationships:

Sewon Kang, MD	Grant/ Research Support: Galderma Intellectual Property, Co Inventor of IP owned by University of Michigan

Members of the planning team have nothing to disclose nor do they have any vested interests or affiliations. **It is the policy of the Chicago Dermatological Society and Colorado Foundation for Medical Care (CFMC) that the faculty discloses real or apparent conflicts of interest relating to the topics of the educational activity, and also discloses discussions of off-label uses of drugs and devices before their presentation(s).**

University of Illinois at Chicago
Department of Dermatology

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Marie Peterson, MD
Jonathan Pewitt, MD

Second Year

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Carmen Schwartz, MD
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First Year

Amanda Cooper, MD
Eliana Krulig, MD
Adrienne Schupbach, MD
Karl Vance, MD

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Case Presented by Joanne Montgomery, MD
and Michelle Bain, MD

History of Present Illness:
This 6 year old African American male presented with an itchy facial rash which started approximately seven months prior. The eruption began as pink-brown papules around his mouth, and later spread to involve the skin around his eyes, nose, neck, and behind his ears. On further questioning, the patient's mother noted that he also had a history of scaling over his eyelashes and an ocular stye shortly preceding the eruption. The patient was initially treated by an outside dermatologist for eczema with pimecrolimus 1% cream without improvement and biopsy was performed with results suggestive of sarcoidosis. Subsequent treatments included desoximetasone 0.25% ointment, tazarotene 0.1% cream, tacrolimus 0.1% ointment, and three weeks of oral prednisone. The patient's mother noted that the eruption worsened and itching intensified during treatment with prednisone.

Past Medical and Surgical History:
None

Medications:
Desoximetasone 0.25% ointment, tazarotene 0.1% cream, tacrolimus 0.1% ointment

Allergies:
No known drug allergies

Family History:
Mother with eczema and scalp psoriasis and two brothers with asthma

Review of Systems:
The patient had nausea and vomiting one week prior to presentation. He is otherwise healthy and denied fevers, chills, shortness of breath, cough, fatigue, weight loss, or arthralgias.

Physical Examination:
Diffusely over the nose and periorificial areas of the face, including perioral, perinasal, and medial periocular skin, are innumerable, closely-spaced, monomorphic, pink-brown papules on an erythematous base. There is overlying flaking scale in a perioral distribution. Few similar papules are scattered over the forehead and lateral cheeks with extension onto the lateral neck.

Diagnostic Procedures and Tests:
Chest X-ray: PA and lateral views of the chest reveal clear lungs bilaterally. The heart size and pulmonary vasculature are normal. There are no pleural effusions.

Ophthalmological exam: Astigmatism, otherwise within normal limits

Histopathology:
Lower eyelid and lip, skin: Biopsies from both sites show dermal non-caseating granulomas with a few sprinkled lymphocytes. Some of the granulomas are perifollicular in distribution. Intrafollicular neutrophils are identified in one of the two biopsies. The PAS stain for fungi and AFB stain for mycobacteria are both negative.

Diagnosis:
Childhood granulomatous periorificial dermatitis

Treatment and Course:

The patient's current therapy, including topical steroids, was discontinued. He was started on oral erythromycin 320 mg three times daily, metronidazole 0.75% cream once daily, and clindamycin 1% lotion once daily. After two months of therapy, the eruption improved dramatically. After four months of treatment, the rash nearly resolved with few residual papules over his upper cutaneous lip.

Discussion:

Childhood granulomatous periorificial dermatitis was first described in 1970 by Gianotti, et al and has been referred to as Gianotti-type perioral dermatitis, facial Afro-Caribbean childhood eruption (FACE), sarcoid-like granulomatous dermatitis, granulomatous perioral dermatitis, and, most recently, granulomatous periorificial dermatitis. This entity, which occurs in healthy prepubertal children, is thought to be a less common variant of perioral dermatitis. Reported cases are more prevalent in dark-skinned patients including African American, Afro-Caribbean, and Asian children, but light-skinned individuals can also be affected.

Patients present with flesh-colored to yellow-brown papules with variable surrounding erythema and scale primarily in a perioral distribution, with frequent involvement of perinasal and periocular skin. Several cases in the literature also describe extrafacial involvement including the trunk, extremities, scalp, and genitalia. Associated blepharitis and conjunctivitis may occur, but systemic symptoms are typically absent. Similar to classic perioral dermatitis, there appears to be an association between corticosteroid use and this granulomatous variant. Another proposed etiologic mechanism includes a granulomatous response to various topical allergens or irritants.

The differential diagnosis includes sarcoidosis, infection, granulomatous rosacea, lupus miliaris disseminatus faciei, and familial juvenile systemic granulomatosis (Blau Syndrome). Careful assessment for associated signs and symptoms should be made, as the lack of systemic involvement makes sarcoidosis less likely, and aggressive systemic therapy should be avoided. Some believe that childhood granulomatous periorificial dermatitis may predict a tendency towards rosacea; however, patients lack the typical pustules, erythema, telangiectasias, and flushing.

Histology reveals normal hair follicles with a dermal granulomatous infiltrate. Well-formed noncaseating granulomas typically with surrounding lymphocytes, or a more diffuse infiltrate of epithelioid histiocytes, lymphocytes, and giant cells may be seen. Special stains for organisms including acid fast bacilli and fungi are invariably negative.

Childhood granulomatous periorifical dermatitis will spontaneously remit over time, but scarring has been reported and treatment is often undertaken. Oral macrolide or tetracycline therapy has proven to be effective alone or in combination with topical metronidazole, erythromycin, and sulfur-sulfacetamide combinations.

Essential Lessons:

- Childhood granulomatous periorificial dermatitis is an important entity to recognize in prepubertal patients with granulomatous skin eruptions.
- Aggressive systemic therapy and extensive workup in these children should be avoided.

References:

1. Andry P, et al. Granulomatous perioral dermatitis in childhood: eight cases. *Pediatr Dermatol* 1995;12:76.
2. Choi YL, et al. Case of childhood granulomatous periorificial dermatitis in a Korean boy treated by oral erythromycin. *J Dermatol* 2006;33(11):806-8.
3. Misago N, et al. Childhood granulomatous periorificial dermatitis: lupus miliaris disseminatus faciei in children? *J Eur Acad Dermatol Venereol* 2005;19(4):470-3.
4. Urbatsch AJ, et al. Extrafacial and generalized granulomatous periorificial dermatitis. *Arch Dermatol* 2002;138(10):1354-8.

Case # 2

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

History of Present Illness:
This 35 year old male presented with a seven year history of a slowly progressive crusted plaque on his upper lip and nose. The lesion started as a "boil" on the left side of his upper lip that opened, drained, and then slowly healed with doxycycline 100mg twice daily and topical mupirocin. Over time, new bumps and pustules developed at the base of his left nostril with subsequent progression to the right side. He reported associated occasional itching, foul smell, and intermittent swelling of the area. He denied any history of asthma.

Past Medical and Surgical History:
Hypertension, heart palpitations, genital herpes, gastric reflux

Medications:
Valacyclovir, loratadine and pseudoephedrine, lisinopril, carvedilol, amlodipine besylate, doxycycline, calcium, cholecalciferol, lansoprazole, mupirocin 2% ointment, polyethylene glycol

Family History:
No history of sarcoidosis, vasculitides, or autoimmune disorders

Social History:
The patient reports past heavy alcohol use, now reduced to occasional. He denies any snorted illicit drug use. He is an active smoker.

Review of Systems:
The patient reported hoarseness, fatigue, occasional epistaxis, and intermittent knee pain. He denied fever, chills, weight changes, shortness of breath, cough, headache, hemoptysis, or hematuria.

Physical Examination:
Over the left upper cutaneous lip, left and right nostril sills, columella, and alar sidewalls is a centrally eroded irregularly shaped plaque with an erythematous and hyperpigmented border.

Laboratory Data:
The following were positive or abnormal:
Angiotensin converting enzyme 5 u/L (9-67), alkaline phosphatase 230 u/L (40-125), aspartate aminotransferase 60 u/L (10-40), alanine aminotransferase 90 u/L (10-50)

The following were negative or within normal limits:
Basic metabolic panel, complete blood count, antinuclear antibody, anti-neutrophilic cytoplasmic antibody, erythrocyte sedimentation rate, glucose-6-phosphate dehydrogenase, hepatitis A, B and C, histoplasma antigen, blastomyces antigen, coccidioides antibody, rapid plasma reagin, QuantiFERON®-TB Gold test, acid fast bacilli smear, and tissue bacterial, fungal and mycobacterial cultures

Diagnostic Procedures and Tests:
Flexible fiberoptic laryngoscopy: Posterior wall cobblestoning and edema of the epiglottis as well as surface irregularity of the endolarynx supraglottis. There is a possible mass in the right anterior cord which is preventing full contact of the vocal folds which are otherwise appropriately mobile.

Computed tomography, Chest: Numerous subcentimeter to slightly prominent lymph nodes within the mediastinum and visualized upper abdomen. Patchy lower lobe opacities may represent atelectasis or sequela of chronic inflammation.

Liver core needle biopsy: No portal, periportal or lobular inflammation, no steatosis, or fibrosis.

Right middle lobe bronchoalveolar lavage: Inflammatory cells present, negative for malignant cells.

Histopathology:
Left upper cutaneous lip, skin: Early biopsies show diffuse nodular dermal granulomatous inflammation with foreign body granulomas surrounding dilated hair follicles. The overlying epidermis is hyperplastic. This is associated with a dense mixed inflammatory cell infiltrate including eosinophils, neutrophils, and plasma cells. Recent biopsy shows superficial and mid dermal epithelioid granulomatous inflammation, with a small number of lymphocytes in the periphery. Results of the following special stains were all normal or negative: Gomori-Grocott methenamine silver, periodic acid-Schiff, Gram, S100, CD68, CD56, CD1a, Fite-Faraco, Giemsa, Epstein barr virus, herpes simplex virus 1 and 2

Diagnosis:
Idiopathic midline destructive disease

Treatment and Course:
The patient was initially treated with doxycycline 100 mg twice daily along with topical mupirocin ointment. With a working diagnosis of sarcoidosis, prednisone 20 mg daily and plaquenil 200 mg twice daily were added. The patient was unable to tolerate attempted transbronchial biopsy to evaluate lung involvement. The patient noted improvement in his hoarseness. He continues to have slow progression of new papules on the nose and lip that leave atrophic depressed scars.

Discussion:
The differential diagnosis of a midline destructive lesion on the face is extensive including neoplastic, autoimmune, infectious, inflammatory, and trauma induced etiologies. Evaluation requires a careful history and physical exam to look for systemic disease. A history of weight loss, cough, fever, and malaise, as well as trauma can aid in diagnosis. However, symptoms are often non-specific and can include nasal discharge, dryness, epistaxis, obstruction, and facial pain or swelling.

Physical exam findings can further delineate the diagnosis with findings as benign as mild crusting to gross destruction of the nasal architecture. A saddle nose depression of the nasal bridge or septal perforations may be consistent with Wegener's granulomatosis, sarcoidosis, Hansen's disease or cocaine abuse. Purple discoloration of the nasal tip or alar rims may suggest sarcoidosis in the form of lupus pernio. The assistance of otolaryngology to visualize and/or biopsy the nasopharynx can be helpful.

The workup should include appropriate laboratory evaluation for leukocytosis, eosinophilia, antineutrophil antibodies, erythrocyte sedimentation rate, rapid plasma reagin, antinuclear antibodies, and infective serology. Cultures should be taken for aerobic and anaerobic bacteria, fungi, and acid-fast bacteria. Biopsy can further delineate the diagnosis by separating granulomatous, atypical lymphocytic, and other neoplastic processes.

Essential Lessons:
- The differential diagnosis of granulomatous dermatitis of the nasal skin includes infections, sarcoidosis, Wegener's granulomatosis, and trauma induced foreign body reactions.
- Extensive workup with multiple biopsies failed to yield a definitive diagnosis in this patient resulting in idiopathic midline destructive disease as a diagnosis of exclusion.

References:

1. Fuchs HA, Tanner SB. Granulomatous disorders of the nose and paranasal sinuses. *Curr Opin Otolaryngol Head Neck Sur* 2009;17(1):23-7.
2. Parker NP, et al. The dilemma of midline destructive lesions: a case series and diagnostic review. *Am J Otolaryngol* 2010;31(2):104-9.
3. Reed J, et al. Clinical features of sarcoid rhinosinusitis. *Am J Med* 2010;123(9):856-62.
4. Schilder AM. Wegener's Granulomatosis vasculitis and granuloma. *Autoimmun Rev* 2010;9(7):483-7.

Case Presented by Adrienne Schupbach, MD, Sophie Marie Worobec, MD, Edmund Chow, MD, James Feinberg, MD, JD, MPH, and Lawrence S. Chan, MD

Patient A

History of Present Illness:

This 23 year old male presented with a three week history of a facial rash. Initially there was a scaly plaque on his left temple. One week later, he developed numerous, very pruritic papules over his forehead, cheeks, and chin. He had been using hydrocortisone 1% cream and diphenhydramine hydrochloride/zinc acetate cream for five days with no improvement.

Past Medical and Surgical History:

Depression

Medications:

None

Allergies:

No known drug allergies

Family History:

No family history of skin cancer or skin diseases

Review of Systems:

Rhinorrhea and cough one week prior to dermatology visit; no fevers, fatigue, arthralgias, or night sweats

Physical Examination:

There are erythematous, scaly, mildly edematous papules coalescing into plaques on the forehead, nose, cheeks, and chin. These minimally extend onto the frontal and temporal scalp.

Laboratory Data:

The following were negative or within normal limits:
Complete blood count, complete metabolic panel, rapid plasma reagin**,** hepatitis C antibody, antinuclear antibody, lactate dehydrogenase, T and B cell studies

Histopathology:

Right cheek, skin: Multiple sections show active folliculitis. The inflammatory infiltrate consists of lymphocytes and numerous eosinophils. There is prominent follicular spongiosis and mucinosis involving multiple hair follicles. The increased mucin deposit is highlighted by the colloidal iron stain. The immunohistochemical stains for CD3 and CD20 show a predominance of CD3-positive T cells over CD 20-positive B cells. There is no evidence of lymphoid atypia. The stains for CD4 and CD8 show a ratio of T4:T8 of 4:1, within normal range.

Diagnosis:

Follicular mucinosis

Treatment and Course:

The patient was started on triamcinolone 0.025% ointment twice daily to the affected areas. After four days of use, he noted substantial improvement and discontinued the ointment. There was complete resolution of facial lesions at his one month follow-up visit. At that time, he noted a new, erythematous, small plaque on his right arm, which also resolved within days of using the triamcinolone ointment. He did not develop any additional skin lesions over the next six months and remains stable.

Patient B

History of Present Illness:

This 51 year old female presented with a one year history of pruritic nodules on her face. She initially developed a dark spot on her right cheek, which subsequently became nodular. This was followed by similar additional lesions appearing on her face and neck. She was treated with a variety of topical acne vulgaris medications and oral antibiotics including minocycline, amoxicillin/clavulanate potassium, and trimethoprim/sulfamethoxazole without improvement. Prior to presentation, she saw an outside dermatologist who performed a biopsy showing pseudolymphomatous folliculitis with suspicion of possible cutaneous T cell lymphoma.

Past Medical and Surgical History:

Hypertension and hyperthyroidism

Medications:

Lisinopril and methimazole

Allergies:

No known drug allergies

Family History:

No family history of skin cancer or skin diseases

Review of Systems:

Occasional night sweats and sinusitis; no fevers, chills, weight loss, fatigue, arthralgias, or myalgias

Physical Examination:

On the face and neck are multiple, 0.5 to 2 cm, fairly well circumscribed, hyperpigmented patches, plaques, and nodules with follicular prominence. She has leonine facies. Her shoulders, upper back, and chest have scattered, hyperpigmented patches and follicular papules.

Laboratory Data:

The following were negative or within normal limits:
Complete blood count, T and B cell studies, T-cell gene rearrangement, lactate dehydrogenase**,** rapid plasma reagin**,** human immunodeficiency virus antibodies, complete metabolic panel, thyroid stimulating hormone, antinuclear antibody, urinalysis

Imaging Studies:

Positron emission tomography/computed tomography: There is minimally increased activity near the chin, suspicious for known cutaneous lymphoma. There are no other areas suggestive of metastatic disease.

Computed tomography, neck: There is mild diffuse thickening of the skin and multiple enlarged lymph nodes bilaterally.

Histopathology:

Left chin and right cheek, skin: Sections show a dense superficial and deep dermal perivascular and perifollicular infiltrate of predominantly lymphocytes. There is extensive infiltration of lymphocytes within the follicular epithelium, associated with focal mucinous degeneration. Some of the lymphocytes have enlarged nuclei, more open chromatin, and irregular nuclear contours. The colloidal iron stain highlights focal increase of mucin within the follicular epithelium. The immunohistochemical stains for CD3 and CD20 show predominance of CD3-positive T cells with significant folliculotropism. The CD4 and CD8 stains show an increased T4:T8 ratio of approximately 10:1. The CD7 stain shows loss of CD7 in many intrafollicular lymphocytes. The CD5 stain is positive.

Left cervical lymph node: There is reactive follicular and paracortical hyperplasia. There is no morphologic or immunophenotypic evidence of mycosis fungoides or lymphoma.

Diagnosis:
Folliculotropic mycosis fungoides

Treatment and Course:
The patient was started on methoxsalen with ultraviolet A light therapy (PUVA) along with bexarotene gel. Oral bexarotene was added at the appropriate dose of 600 mg daily, but swelling of facial lesions occurred. The patient was then encouraged to start bexarotene 75 mg three times weekly, which she declined. She was treated for a brief time with interferon-alpha injections, but these were discontinued due to depressed mood. She started extracorporeal photopheresis in March, 2010, which has been well tolerated. She is also being treated with betamethasone dipropionate and hydrocortisone valerate ointments topically. She initially noted some softening and flattening of her facial lesions. However, she continues to develop new plaques and nodules on her face, trunk, and arms.

Discussion:
Follicular mucinosis (FM) is an uncommon inflammatory disorder characterized clinically by indurated plaques, usually on the head and neck. Less commonly, FM appears as generalized or localized, grouped, follicular, keratotic plugs on the trunk, proximal limbs, face, and scalp. If FM lesions are associated with alopecia, the condition is known as alopecia mucinosa. FM occurs either as a primary idiopathic condition or as a secondary disorder associated with various benign or malignant diseases. Primary follicular mucinosis, also known as Pinkus' follicular mucinosis, usually occurs in children and young adults and is often characterized by spontaneous regression.

Secondary FM often occurs in older adults, has more of a generalized distribution, and is characterized by a chronic relapsing/remitting course. Secondary follicular mucinosis can be associated with numerous benign conditions including atopic dermatitis, arthropod bites, alopecia areata, and lupus erythematosus. It can also be secondary to various lymphoid neoplasms, most notably cutaneous T cell lymphoma (CTCL). Association with chronic lymphocytic leukemia, leukemia cutis, acute myelogenous leukemia, cutaneous B-cell lymphoma, and Hodgkin's disease has been reported. There is no specific treatment for FM, and close monitoring for the development of CTCL is recommended in cases of apparent primary FM. In the case of secondary FM, treatment of the underlying disease is indicated.

FM is characterized histologically by mucin within the epithelium of the follicular outer root sheath and sebaceous glands, and there is dissolution of keratinocytes. The mucin can be highlighted by alcian blue or colloidal iron stains. A variable inflammatory infiltrate of lymphocytes, histiocytes, and eosinophils is seen. Differentiation between primary FM and secondary FM associated with CTCL can be difficult, and multiple biopsies may be needed.

Folliculotropic CTCL (FCTCL) is a variant of mycosis fungoides (MF) characterized by folliculotropic infiltrates of atypical lymphocytes, generally with sparing of the epidermis. There is often associated secondary FM. FCTCL makes up approximately 10% of cases of MF. It most commonly occurs in adults, although it rarely may affect children and adolescents. Men are more often affected by FCTCL than women. FCTCL presents as acneiform lesions, comedones, cysts, and alopecic patches, plaques, and nodules with preferential involvement of the head and neck. Pruritus is common.

FCTCL is often resistant to therapy and generally carries a poorer prognosis than epidermotropic CTCL. There is no specific treatment of choice. Available therapies include bexarotene, total skin electron-beam therapy, localized radiation, extracorporeal photopheresis, interferon, vorinostat, pralatrexate, PUVA, EPOCH therapy (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) and stem cell transplant. While most therapies work via immunosuppression, stem cell transplantation generates a graft versus tumor response.

Essential Lessons:

- Follicular mucinosis occurs either as a primary idiopathic condition or as a secondary disorder in association with benign or malignant disease, most notably cutaneous T cell lymphoma.
- Folliculotropic cutaneous T cell lymphoma commonly pursues an aggressive course and is more resistant to therapy than the epidermotropic variant.

References:

1. Akpek G, et al. Chemotherapy with etoposide, vincristine, doxorubicin, bolus cyclophosphamide, and oral prednisone in patients with refractory cutaneous T-cell lymphoma. *Cancer* 1999; 86(7):1368-76.
2. Apisarnthanarax N, et al. Mycosis fungoides with follicular mucinosis dis*playin*g aggressive tumor-stage transformation. *Am J Clin Dermatol* 2003;4(6):429-35.
3. Bonta MD, et al. Rapidly progressing mycosis fungoides presenting as follicular mucinosis. *J Am Acad Dermatol* 2000;43(4):635-40.
4. Clark-Loeser L, Latkowski J. Follicular mucinosis associated with mycosis fungoides. *Dermatol Online J* 2004;10(3):22.
5. Gerami P, et al. Folliculotropic mycosis fungoides: an *aggressive variant of c*utaneous T-cell lymphoma. *Arch Dermatol* 2008:144(6):738-46.
6. Ito T, et al. Folliculotropic mycosis fungoides and a leonine clinical appearance of the face. *Dermatol Online J* 2008;14(9):6.
7. Lehman JS, et al. Folliculotropic mycosis fungoides: single center study and systemic review. *Arch Dermatol* 2010;146(6):662-4.
8. Van Doorn R et al. Follicular mycosis fungoides, a distinct disease entity with or without associated follicular mucinosis: a clinicopathologic and follow-up study of 51 patients. *Arch Dermatol* 2002;138(2):191-8.
9. Willemze R. Cutaneous T-cell lymphoma *in* Dermatology. Second Edition. Bolognia JL editor in chief. Spain: Mosby Elsevier, 2008:1875-6.

Case # 4

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

UNKNOWN CASE

This 68 year old female presented with a rash on her left breast.

Case # 5

Case Presented by Karl Vance, MD,
Shelley Halper, MD, and Iris K Aronson, MD

History of Present Illness:
This 76 year old Caucasian male presented with sixteen months of bullae formation at sites of minor trauma. Multiple biopsies performed by Dr. Halper were suggestive of bullous pemphigoid, though initial work up was inconclusive. Treatment with prednisone taper, tetracycline, niacinamide, and desoximetasone 0.25% ointment decreased, but did not eliminate the appearance of new lesions. Past medical, surgical, and family histories were non-contributory and he has no known drug allergies.

Medications:
Prednisone, tetracycline, niacinamide, desoximetasone 0.25% ointment, aspirin, simvastatin, furosemide, fluticasone propionate and salmeterol inhalation powder

Review of Systems:
The patient reported progressive dysgeusia occurring approximately with the development of bullae. He denied weight loss, fever, chills, arthralgias, vision changes, dysuria, or dysphagia.

Physical Examination:
June 2010: Several tense bullae, superficial erosions, and hemorrhagic crusts are seen on the bilateral extensor elbows and knees, palms, soles, and buttocks, with scarring and milia at sites of prior bullae. A few superficial erosions are noted on the oral mucosa.

October 2010: In addition to the above findings, large coalescing, erythematous plaques with serpiginous heaped up borders and central clearing are noted in the bilateral axillae and buttocks.

Laboratory Data:
The following were negative or within normal limits:
Complete blood count, complete metabolic panel, glucose-6-phosphate dehydrogenase level, antinuclear antibody, thiopurine methyltransferase, urine porphobilinogen concentration, ELISA for BP180 antibody and BP230 antibody.

Histopathology/Immunopathology:
H&E, early lesions: foot and elbow, skin: Biopsies from both sites show similar findings. There is subepidermal vesiculation, associated with perivascular and interstitial dermal infiltrate of lymphocytes and a few eosinophils.

H&E, new eruption: left axilla, skin: There is subepidermal vesiculation associated with a mixed dermal inflammatory cell infiltrate including lymphocytes, eosinophils, and numerous neutrophils. Some of the neutrophils are clustered in the dermal papillae.

Direct immunofluorescence: 1. Foot, perilesional skin: IgG in a smooth band at the interface, IgA, IgM and C3 in a coarse granular band at the interface, and vascular deposition of IgM and C3; 2. Elbow, perilesional skin: IgG and C3 on the roof and base of subepidermal blister, IgM in colloid bodies; Immunoperoxidase staining for collagen type IV showed linear deposition on the roof of the blister; 3. Left axilla (new eruption), perilesional skin: Linear deposition at the basement membrane zone of IgG, IgM, IgA and C3.

Indirect immunofluorescence: Monkey esophagus showed IgG epithelial cell surface binding autoantibodies at the basement membrane zone at a titer of 1:320. Human salt split skin showed IgG antibodies on the dermal side of the split at a titer of 1:1280.

Diagnosis:
Epidermolysis bullosa acquisita: mechanobullous type, with progression to inflammatory type

Treatment and Course:
The patient continued on low dose prednisone and niacinamide, but was switched from tetracycline to doxycycline with new lesion formation. Tetracycline was reinstated. Colchicine was added and the patient inadvertently stopped his other three medications resulting in the inflammatory lesions in his axillae. Colchicine was discontinued after he developed nausea and dizziness, and low dose dapsone was started. Serum was collected to delineate the specific antigenic targets of IgG, IgM and IgA, and these results are pending.

Discussion:
Epidermolysis bullosa acquisita (EBA) is a rare, subepidermal, autoimmune bullous disease that results from IgG autoantibodies to collagen type VII. Diagnostic criteria rely on exclusion of other bullous diseases as well as clinical resemblance to hereditary dystrophic epidermolysis bullosa and demonstration of subepidermal blister with IgG localized to the sublamina densa. The classic mechanobullous form clinically may resemble porphyria cutanea tarda with new lesions occurring at sites of minor trauma with scarring and milia. Inflammatory EBA may resemble bullous pemphigoid, linear IgA disease, mucous membrane pemphigoid, or Brunsting-Perry pemphigoid.

Patients with a confirmed diagnosis of an inflammatory autoimmune blistering disease may develop new clinical features or become resistant to previously successful treatment. The theory of epitope spreading proposes that the initial autoimmune response reveals new self-antigens that were previously hidden from the immune system. This may lead to the development of auto-antibodies to a new epitope on either the same or a different, often associated, protein. The primary epitope in EBA is the noncollagenous (NC)-1 domain of type VII collagen, though recent research has proposed that epitopes within the triple helix (T-H) domain may be associated with the rarer, inflammatory form.

EBA is difficult to treat and often has a long clinical course with potential long term complications including blindness, esophageal stricture, and joint contractures. Treatment options are largely based on case reports and series as there is a paucity of randomized, controlled therapeutic trials. EBA is often refractory to high dose steroids, and successful treatment with colchicine, dapsone, cyclosporine, mycophenolate mofetil, extracorporeal phototherapy, intravenous immunoglobulin, and rituximab has been reported.

Essential Lessons:
- EBA is a rare autoimmune blistering disease with IgG antibodies to collagen VII, with variants including the classic mechanobullous form as well as a clinically diverse inflammatory form.
- Multiple, distinct clinical presentations in one patient may be due to formation of multiple antibodies, which can be explained by the process of epitope spreading.

References:

1. Fairley J, et al. A patient with both bullous pemphigoid and epidermolysis bullosa acquisita: an example of intermolecular epitope spreading. *J Am Acad Dermatol* 2004;51(1):118-122.
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Case # 6

Case Presented by Shruthi Reddy, MD,
Lucy Wisdom, MD, and Iris Aronson, MD

History of Present Illness:
This 28 year old Caucasian female presented in June of 2006 at age 24 with a diagnosis of pemphigus vulgaris made at the Mayo Clinic with oral and skin blisters on the trunk and scalp. At presentation, she was on 60 mg of prednisone daily. She was started on mycophenolate mofetil as a steroid sparing agent, and her dose was increased up to 2 grams per day when she developed a hypersensitivity syndrome associated with cytomegalovirus infection (presented at CDS 2006). After recovery from the hypersensitivity syndrome, azathioprine was started and increased up to 200 mg per day without much improvement. Azathioprine was discontinued with the development of hepatotoxicity. She continued on prednisone for one year until developing avascular necrosis of the hip requiring a hip replacement. The patient was then given three monthly treatments of intravenous immune globulin (IVIG) with persistence of lesions. In October 2007, the New England Journal of Medicine October 2006 protocol of rituximab and IVIG was initiated. After recurrence in 2008, another course of rituximab and IVIG was repeated. She was off all medications when she discovered she was pregnant in December 2009 despite having an intrauterine device.

Past Medical and Surgical History:
Pemphigus vulgaris, avascular necrosis of the hip status post hip replacement, cytomegalovirus infection, hypersensitivity syndrome to mycophenolate mofetil, abnormal liver enzymes with azathioprine

Medications:
None

Allergies:
Mycophenolate mofetil and azathioprine

Social History:
Married with no children until birth of a baby boy in July 2010

Family History:
Grandfather with melanoma at age 45 and paternal aunt with rheumatoid arthritis

Review of Systems:
She reported nausea and decreased energy for a few weeks before her pregnancy was discovered and denied fevers, chills, vomiting, arthralgias, or myalgias.

Physical Examination:
There are a few, small yellow scaly plaques over the crown of the scalp and several scattered erosions on her chest with multiple oval, hyperpigmented patches throughout her neck, trunk and arms.

Histopathology/Immunopathology:
H&E, right upper abdomen, skin (2006-Mayo Clinic): Neutrophil rich, subcorneal and intragranular cleft and acantholysis.

Direct immunofluorescence, upper abdomen, skin (2006-Mayo Clinic): Strong epidermal cell-surface deposition of IgG and C3, weak epidermal cell-surface deposition of IgA, negative IgM and fibrinogen.

Indirect immunofluorescence, monkey esophagus: Positive at 1:20 (4/2007) and negative (8/2009)

Diagnosis:
Pregnancy after rituximab and intravenous immune globulin for pemphigus vulgaris

Treatment and Course:
The patient continued to develop a few scaly lesions on her scalp and a few erosions on her chest which were controlled with doxycycline and topical steroids after the rituximab and IVIG treatments. She remained off all medications throughout her pregnancy with no blisters and delivered a healthy boy in July 2010.

Discussion:
Pemphigus vulgaris (PV) is a rare autoimmune blistering disease due to desmoglien 3 and 1 autoantibodies. PV in pregnancy is even rarer with less than 50 cases documented. Severe maternal disease and high antibody titers can lead to poor neonatal outcomes (fetal growth restriction, preterm births, premature labor, premature rupture of membranes, stillbirths, or intrauterine fetal death). Transplacental transmission of IgG antibodies may result in pemphigus lesions in the neonate which tend to improve spontaneously.

First line treatment for PV during pregnancy is corticosteroids. Prednisone crosses the placental barrier less than other steroids. High levels of steroids, however, have been associated with adverse fetal outcomes with no increase in congenital malformations. Azathioprine, pregnancy category D, is typically used for PV and has been used to treat other conditions during pregnancy without fetal harm. However, infections, aplasia cutis congenita, and poor neonatal outcomes with a low risk of congenital malformations have been reported. Mycophenolate mofetil (MMF) is teratogenic in rats and rabbits and has been shown to cause craniofacial and cardiovascular malformations, kidney defects, and digital anomalies in transplanted women exposed to MMF in their first trimester.

An attempt should be made to taper and discontinue immunosuppressive medications in young women who wish to conceive, but this may lead to severe pemphigus reactivation. Rituximab is a humanized monoclonal antibody against CD20, a B-cell antigen thought to deplete pathogenic antibody producing B cells and eliminate the production of pathogenic autoantibodies. IVIG is used both for therapeutic functions and to protect from infections associated with reduced immunoglobulin levels. Although long-term remission with minimal treatments of rituximab and IVIG has been established, recurrences occur regularly, usually about one year post treatment. Rituximab and IVIG may be a significant therapeutic advantage in young women with PV who wish to become pregnant or are pregnant as it appears to be safe during pregnancy.

Essential Lessons:
- Pemphigus vulgaris and treatment for PV during pregnancy may result in poor fetal outcomes.
- Rituximab and IVIG should be kept in mind as a treatment option for women who wish to conceive.

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Case # 7

Case Presented by Carmen Schwartz, MD,
Edmund Chow, MD, and Iris Aronson, MD

History of Present Illness:
This 20 year old male presented at age 17 with a five month history of a rash over the face, scalp, and chest. The eruption began on his cheeks and initially looked like a red, blistering sunburn that was itchy and sometimes painful. In the 2 months prior to presentation, the eruption became progressively darker in color. Prior treatments included salicylic acid shampoo, ciclopirox shampoo, fluticasone 0.05% lotion, and doxycycline.

Past Medical and Surgical History:
Ostectomy of left calcaneonavicular bony bridge with an extensor digitorum brevis muscle interposition

Medications:
Tacrolimus 0.1% ointment, fluocinolone 0.01% oil, and ibuprofen as needed for foot pain

Allergies:
No known drug allergies

Family History:
No history of skin diseases or cancer

Review of Systems:
He denied fevers, chills, weight loss, oral erosions, shortness of breath, arthralgias, or fatigue.

Physical Examination:
Throughout the scalp are scattered, thick, verrucous plaques. Diffuse, hyperpigmented plaques with adherent scale are noted over malar cheeks, spreading to the forehead and chin. There are multiple, hyperpigmented papules and plaques over the trunk and extremities with scattered erosions.

Laboratory Data:
The following were positive or abnormal:
Glucose-6-phosphate dehydrogenase level 3.7 u/g Hb (7-20.5), thiopurine methyltransferase level 39.2 u/mL (15.1-26.4)

The following were negative or within normal limits:
QuantiFERON®-TB Gold test, complete blood count with differential, comprehensive metabolic panel, antinuclear antibody, urinalysis

Immunodermatology:
ELISA: IgG desmoglein 1 antibodies 214 units (nl <14 units), IgG desmoglein 3 antibodies 1 unit (nl <9 units)

Histopathology/Immunopathology:
H&E, left chest, skin: Multiple sections show intraepidermal vesiculation beneath the granular layer, associated with acantholytic dyskeratosis. There is also mild dermal infiltrate of lymphocytes and a few melanophages.

Direct immunofluorescence, perilesional skin: There is strong speckled deposition of IgG and C3 on keratinocyte cell surfaces. IgM is positive with few speckles and granules noted at the basement membrane zone. IgA and fibrin are not detected.

Indirect immunofluorescence, human skin: IgG epithelial cell surface binding at titer 1:5120 (1/2010)

Indirect immunofluorescence, monkey esophagus: IgG epithelial cell surface binding at titer 1:5120 (1/2010), >1:1280 (8/2008), and 1:160 (1/2008)

Diagnosis:
Pemphigus foliaceus

Treatment and Course:
Treatment began with mycophenolate mofetil (MMF) 500 mg daily with subsequent increases to a total dose of 3 g daily. He continued the topicals noted above, and high SPF sun protection (SPF 85-100) was added. He initially saw improvement with flattening of the lesions but had continued, worsening outbreaks on the body and diffuse, dark hyperpigmentation. MMF was discontinued and prednisone and azathioprine were started. Azathioprine was titrated up to 200 mg daily. Hydroxychloroquine was also added. He continues to have waxing and waning of his disease without adequate control. Cyclophosphamide was discussed, but not utilized due to serious, long term, permanent side effects. There has been discussion regarding treatment with rituximab and intravenous immunoglobulin (IVIG).

Discussion:
Pemphigus foliaceus (PF) is an autoimmune blistering disease characterized by IgG autoantibodies against the intercellular adhesion molecule desmoglein 1. Desmoglein 1 is primarily expressed in the granular layer of the epidermis, thus acantholysis and blister formation occurs in the upper epidermis with resultant superficial erosions.

PF is characterized by a chronic course without involvement of the mucous membranes. Crusted plaques and erosions are most commonly found in a seborrheic distribution. Triggering factors for PF include ultraviolet light exposure, medications, and infections. PF may often be misdiagnosed in the younger population as bullous impetigo, seborrheic dermatitis, eczema, psoriasis, or staphylococcal scalded skin syndrome. Cases of hyperkeratotic, verrucous, pigmented plaques resembling acanthosis nigricans or seborrheic keratoses developing within pemphigus erosions have been reported. The etiology of this remains unclear. Possibly, long lasting epidermal injury in refractory erosions results in an excessive proliferative response.

Many patients with PF may note initiation or exacerbation after UV exposure. Epidermal IgG and complement deposition have been demonstrated in the normal-appearing skin of pemphigus patients after UV exposure. The precise mechanism is not known, but may be due to epithelial antigen modification and subsequent antibody recognition. Hydroxychloroquine has been used as an adjuvant therapy for patients with persistent and widespread photosensitive disease.

The mainstay of treatment for PF is systemic steroids. However, almost all patients will require some type of steroid sparing immunosuppressant for treatment. These include azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, dapsone, hydroxychloroquine, methotrexate, cyclosporine, and IVIG.

Essential Lessons:
- Pemphigus foliaceus is an autoimmune blistering disease caused by the development of antibodies directed against the desmosomal adhesion protein desmoglein 1.
- Marked hyperpigmentation seen in some pemphigus foliaceus lesions may require intensive immunosuppression and scrupulous sun avoidance.

References:

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6. Usui K, et al. Pemphigus vulgaris associated with transient acanthosis nigricans like lesion. *J Dermatol* 1998;25:550-2.

Case # 8

Cases Presented by Eliana Krulig, MD
and Iris Aronson, MD

History of Present Illness:
This 47 year old female presented with a one year history of tender, itchy, pink lesions on her hands. She had significant joint pain, but no muscle weakness. Biopsy was performed at an outside institution with results suggestive of dermatomyositis. Subsequent treatment included low dose oral prednisone and methotrexate. The patient experienced hair loss, so methotrexate was stopped and weekly adalimumab was initiated. Her clinical course fluctuated with improvement in the joint pain but worsening of the skin lesions. The patient was referred to University of Illinois for further management. Hydroxychloroquine was added to the existing regimen, but an erythematous rash and hair loss led to discontinuation after two weeks. Later, the patient developed purple net-like patches on her back and shoulders, crusted ulcerations on her back, and subcutaneous nodules on her left third finger.

Past Medical and Surgical History:
Rheumatoid arthritis (rheumatoid factor positive)

Medications:
Adalimumab, prednisone

Allergies:
Adverse reactions to methotrexate (hair loss) and hydroxychloroquine (rash, hair loss)

Family History:
Mother with Crohn's disease, paternal grandmother with early onset hand arthritis

Review of Systems:
The patient reported muscle weakness and joint pain. She denied fevers, chills, night sweats, or weight loss.

Physical Examination:
Over the bilateral malar cheeks are symmetrical erythematous patches. Violaceous thin papules are noted over the metocarpophalangeal joints and some of the proximal interphalangeal and distal interphalangeal joints. The proximal nail folds are erythematous with ragged cuticles. Over the palmar surfaces including the interphalangeal joints, but sparing the skin in between, are hyperkeratotic pits and erythematous scaling papules. There are reticulated purple patches over the trunk and necrotic ulcerations with thick overlying crust on the back and shoulders. Subcutaneous white nodules are noted around the left third distal interphalangeal joint.

Laboratory Data/Diagnostic Procedures and Tests:
The following were negative or within normal limits:
Complete blood count with differential, complete metabolic panel, creatine kinase, aldolase, urinalysis, antinuclear antibody, anti-double stranded DNA antibody, anti-Smith antibody, anti-ribonucleoprotein antibody, anti-SSA antibody, anti-SSB antibody, anti-Jo1 antibody, iron, thyroid stimulating hormone, Ca-125, C3, C4, CH50, cryoglobulins, anti-cardiolipin IgG, IgM, and IgA, anti-phospholipid IgG, IgM, and IgA, pelvic ultrasound, mammogram, pulmonary function tests

Histopathology:
Left fourth finger, skin: Multiple sections show interface vacuolar dermatitis associated with superficial dermal edema and perivascular dermal infiltrates of lymphocytes. There is mild psoriasiform epidermal hyperplasia and increased parakeratosis.

Diagnosis:
Dermatomyositis and rheumatoid arthritis overlap complicated with vasculitis and calcinosis cutis

Treatment and Course:
The patient was started on rituximab, receiving two infusions two weeks apart, with rapid improvement of all her skin lesions, arthralgias, and myalgias. She continued a treatment regimen of rituximab every five months and low dose prednisone daily with near complete resolution of her skin involvement and a sustained significant improvement of her muscle and joint symptoms. Although there has been no further progression of her cutaneous calcification, the existing lesions persist, creating a therapeutic challenge.

Discussion:
Dermatomyositis (DM) is a chronic inflammatory connective tissue disease characterized by typical skin findings with or without myositis. Skin manifestations include diffuse erythema, Gottron's papules or sign, heliotrope rash, poikiloderma, pruritus, photosensitivity, and periungual changes, among others. Myositis is recognized mainly as symmetric proximal muscle weakness, or simply fatigue.

The etiology of DM is unclear, but recent evidence suggests that humoral immunity may play a role. Up to 30% of adult DM cases are associated with malignancy, therefore periodic thorough malignancy screening is recommended. Patients with concomitant vasculitis may have a higher risk of developing a malignancy. DM can be associated with interstitial lung disease and vascular involvement, as well as overlap syndromes with other mixed connective tissue diseases. Complications may arise from the vascular and muscular involvement, or from dystrophic calcification. Calcification is more common in the juvenile form of DM, but can also occur in the adult form. This complication, which occurs primarily on the upper half of the body, is related to disease duration and severity.

Evaluation of DM patients should include serum muscle enzymes, autoantibody tests, and malignancy work up. Muscle enzymes, such as creatine kinase and aldolase, tend to be elevated if myositis is present, but the degree of muscle dysfunction may be much greater than the enzyme levels suggest. Muscle weakness with relatively normal enzyme levels can also occur. Autoantibodies, albeit not always present, are found in a majority of DM patients and can aid in the diagnosis of overlap syndromes and in determining prognosis. Pulmonary functions must also be evaluated.

Systemic steroids are the mainstay treatment for DM. Initial aggressive therapy is recommended when myositis is present to avoid serious complications and chronic disability. Second line agents are chosen depending on treatment target. For skin disease, in addition to strict sun protection, hydroxychloroquine, methotrexate (MTX) and intravenous immunoglobulin (IVIg) have been used successfully. For muscle disease, in addition to exercise and physical therapy, MTX, mycophenolate mofetil, azathioprine, cyclosporine, cyclophosphamide, IVIg, and biologics, such as rituximab, are therapeutic options. For calcinosis, alternatives include surgical excision, diltiazem, probenecid, and alendronate.

Essential Lesson:
- Therapy for dermatomyositis should be started early in the disease course in order to avoid severe complications.

References:

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Case # 9

Case Presented by Amanda Cooper, MD
and Sophie Marie Worobec, MD

History of Present Illness:
This 64 year old female presented with asymptomatic, dark brown spots since June 2008. Initially located on her neck, the lesions then spread to involve her face, arms, hands, trunk, and legs. The lesions began after starting lisinopril and Levoxyl® 75 mg (purple pill) which were later changed to metoprolol and Synthroid® 50 mg (dye free), respectively. Following these changes, the lesions were stable for several months; however, she now continues to develop new lesions. She has tried several topical steroids and topical fluocinolone/hydroquinone/tretinoin without any improvement.

Past Medical and Surgical History:
Hypothyroidism following radioactive iodine for hyperthyroidism, deep venous thrombosis, hypertension, hypercholesterolemia, gastritis, and tubal ligation

Medications:
Levothyroxine (Synthroid®), metoprolol, omega-3-acid ethyl esters, vitamin D, and naproxen

Allergies:
Sulfates

Family History:
No skin diseases. Ethnicity: Spanish European, Asian Indian, African, and Taino Indian

Review of Systems:
She reported headaches and difficulty sleeping. She denied joint pain, shortness of breath, or chest pain.

Physical Examination:
There are multiple dark brown macules and patches over her face, neck, axillae, arms, dorsal and palmar hands, chest, back, abdomen, and legs. A few of the hyperpigmented macules on her neck and axillae also had slight erythema and scale on initial presentation. Oral mucosa, teeth, and nails were unremarkable.

Laboratory Data:
The following were positive or abnormal:
Erythrocyte sedimentation rate 30 mm/hr (0-20), absolute eosinophils 1.6 k/µL (0.1-0.5), thyroid stimulating hormone 6.20 mIU/mL (0.35-5)

The following were negative or within normal limits:
Antinuclear antibody, complete metabolic panel, hepatitis panel, morning cortisol, adrenocorticotropic hormone, stool for ova and parasites

Histopathology/Immunopathology:
H&E, left neck and left axilla, skin: Both biopsies show similar changes. Multiple sections show lichenoid interface dermatitis associated with superficial dermal infiltrate of lymphocytes and melanophages. In one biopsy the epidermis is atrophic. PAS stain highlights normal appearing basement membrane without evidence of fungal elements.

Direct immunofluorescence, left neck, lesional skin: Huge groups of cytoids stain positive for IgG, IgM, IgA, and C3.

Diagnosis:
Lichen planus pigmentosus

Treatment and Course:
The patient used tacrolimus 0.1% ointment topically for several months without improvement. She underwent spot testing with a 532 nm laser, but did not have resolution of pigment and did not wish to retry treatment. Recently, she was started on low-dose low-molecular-weight heparin at 3 mg subcutaneously weekly. Work-up by a hematologist for her eosinophilia, including a bone marrow biopsy, did not identify any abnormalities. There was consideration that her lesions may have been drug-induced by lisinopril, naproxen or the dye in Levoxyl® 75 mg (blue #1, red #30); however, the above medications have been discontinued (lisinopril and naproxen in June 2008; Levoxyl® 75 mg in February 2010) and her lesions continue to progress.

Discussion:
Lichen planus pigmentosus (LPP) is a rare variant of lichen planus (LP) characterized by dark brown to gray macules in sun-exposed and intertriginous areas. Patients may also exhibit a more generalized reticulate pigmentation and involvement of the mucous membranes. Most LPP cases have been reported in patients from Latin America, India, the Middle East, and other Asian countries. Histologically, LPP is characterized by epidermal atrophy, a lichenoid dermal infiltrate with vacuolar degeneration of the basal cell layer, cytoid bodies, and pigment incontinence.

The differential diagnosis of LPP includes a lichenoid drug eruption (LDE). Clinical examination and histopathology typically cannot distinguish the two. Causes of LDE include beta-blockers, angiotensin-converting enzyme inhibitors, penicillamine, antimalarials, nonsteroidal anti-inflammatory drugs, gold, lithium, and methyldopa. Also included in the differential diagnosis of LPP is erythema dyschromicum perstans (EDP), otherwise known as 'ashy dermatosis.' EDP is characterized by gray to blue macules and patches that may initially have a raised, erythematous border. The histopathology is similar to that of LPP, but lacks a lichenoid infiltrate. Additionally, patients with EDP present at an earlier age (1st to 3rd decade) and lesions typically spare the oral mucosa, palms, and body folds.

There have been several reports of successful treatment of LP with low-molecular-weight heparin.

Essential Lessons:
- Lichen planus pigmentosus is a very rare variant of lichen planus that is characterized by dark brown macules or patches and a lichenoid infiltrate with interface changes and pigment incontinence.
- Low-molecular-weight heparin has been reported to be effective in some cases of lichen planus.

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**Cases Presented by Brendan Thomas, MD, Eugene Mandrea, MD,
Claudia Hernandez, MD, Sophie Marie Worobec, MD, and Aleksandar Krunic, MD, PhD**

Patient A

History of Present Illness:

This 65 year old male presented in late 2008 with an approximately one year history of eyelid swelling that tended to wax and wane. The swelling was associated with occasional itching and burning.

Past Medical and Surgical History:

Rosacea, blepharoplasty two years prior, cataract surgery twenty years prior, pacemaker placement, knee surgery, anxiety, depression

Medications:

Escitalopram, clonazepam, mirtazapine, varenicline

Allergies:

No known drug allergies

Family History:

Mother with colon cancer

Social History:

The patient admitted to smoking approximately six cigarettes per day for more than twenty years but denied any alcohol or illicit drug use.

Physical Examination:

The forehead and bilateral superior periorbital skin were characterized by firm, pink to red, rolled plaques. There was edema of the bilateral lower eyelids, with the left more pronounced than the right. The nose was bulbous in appearance with scattered open comedones across the nose and bilateral malar surfaces.

Laboratory Data:

The following were negative or within normal limits:
Complete blood count with differential, basic metabolic panel, liver function tests, total protein and albumin, antinuclear antibody, thyroid stimulating hormone, free thyroxine, fasting lipid panel

Histopathology:

Left forehead, skin: Multiple sections of the left forehead biopsy show perifollicular mixed inflammatory cell infiltrate including lymphocytes, histiocytes, and a few neutrophils. There is significantly increased dermal edema. There is no evidence of epidermotropism or interstitial infiltrate of the lymphocytes. The Periodic acid-Schiff stain highlights a normal appearing basement membrane with no evidence of fungal elements.

Diagnosis:

Persistent edema of rosacea

Treatment and Course:
The patient was first treated with an approximately three month course of doxycycline 100 mg twice daily, along with cetirizine 10 mg nightly for symptomatic relief. When there was no improvement, the the doxycycline was discontinued and a course of oral isotretinoin 40 mg daily was initiated. The dose was slowly titrated up to 60 mg daily with no complications except a slight increase in serum triglycerides (peak value 376). During the course of isotretinoin, the patient continued the nightly cetirizine and was also started on amoxicillin 500 mg twice daily, along with daily dapsone 5% gel, desonide 0.05% ointment, and sodium sulfacetamide 10% lotion to the affected areas. Initially, the patient noted only modest improvement in the swelling. However, after seven months of therapy with a total cumulative dose of approximately 9,000 mg of isotretinoin, his facial swelling had improved significantly. The patient stopped all the above therapies except the sodium sulfacetamide 10% lotion.

Patient B
History of Present Illness:
This 57 year old male presented in early 2009 with an approximately one year history of swelling and redness around the eyes, associated with occasional itching. The swelling was worse in the morning and evening when lying down and was often exacerbated by heat. He had been evaluated by otolaryngology and allergy/immunology and treated with several courses of prednisone with only modest improvement in the redness and minimal change in the swelling. He had also been treated with multiple courses of oral amoxicillin, doxycycline, azithromycin, and hydroxychloroquine, as well as topical metronidazole and azelaic acid, with minimal improvement.

Past Medical and Surgical History:
Recurrent herpes simplex virus infection on the nose, hypertension, hyperlipidemia, sinus surgery for a history of chronic sinusitis, lower back surgery

Medications:
Famciclovir as needed, olmesartan, rosuvastatin

Allergies:
No known drug allergies, allergy to iodine contrast medium

Family History:
Sister with rosacea

Social History:
No tobacco, alcohol, or illicit drug use

Physical Examination:
The periorbital skin was edematous with a pronounced red discoloration of the infraorbital areas bilaterally. There was no conjunctival injection or facial scaling, but a few small telangiectasias on the nose were noted.

Laboratory Data:
The following were positive or abnormal:
Antinuclear antibody 1:160, speckled pattern

The following were negative or within normal limits:
Complete metabolic panel, fasting lipid panel, thyroid stimulating hormone, rheumatoid factor, Ro and La antibodies, RNP antibody, Smith antibody, double stranded DNA antibody, Jo-1 antibody, antiphospholipid antibody panel, lupus anticoagulant, thyroid peroxidase antibody, thyroglobulin antibody, myeloperoxidase antibody, proteinase 3 antibody, C4, c1 esterase inhibitor level and function

Diagnostic Procedures and Tests:
Patch testing with the North American series, as well as several of the patient's own skin care products, was notable for reactions to benzoic acid, carbamates mix, Euxyl K 400, nickel sulfate hexahydrate, neomycin sulfate, and azelaic acid 15% (Finacea) gel manufactured by Intendis

Dimethylglyoxime testing of the patient's eyewear was negative

Prick testing was negative

Histopathology:
Right malar cheek, skin: Biopsy shows perifollicular infiltrate of lymphocytes and histiocytes, associated with small dilated blood vessels in the superficial dermis. There is slight dermal fibrosis.

Diagnosis:
Persistent edema of rosacea

Treatment and Course:
The patient initially underwent patch testing with the above reactions noted and was subsequently encouraged to avoid all known allergens. After six weeks of known allergen avoidance, the patient noted no change in the periorbital edema. Therefore, he was started on doxycycline 100 mg twice daily, along with dapsone 5% gel twice daily to be applied to the affected areas only after performing one week of repeat open application testing (ROAT). However, after two months, the patient reported slight worsening of his edema and his therapy was changed to amoxicillin 1000 mg twice daily with twice daily application of both 10% sodium sulfacetamide and 4% sulfur (Sumaxin) cleansing pads and desonide 0.05% gel. After one month, he reported only 25% improvement, and isotretinoin 40 mg twice daily was added to the therapeutic regimen. Soon after, he developed mild facial skin and lip dryness and discontinued the topical therapies while continuing on the oral amoxicillin and isotretinoin. The isotretinoin was continued for approximately ten months, reaching a cumulative dose of 21,200 mg, after which he noted a significant improvement in his facial redness and swelling.

Discussion:
Persistent edema of rosacea is an uncommon cutaneous condition characterized by a hard, nonpitting edema restricted to the forehead, glabella, upper eyelids, nose, and cheeks. This condition is also known as chronic upper facial erythematous edema, Morbihan's disease, morbus Morbihan, and rosaceous lymphedema. Despite the name, it is unclear whether this condition is a distinct disease or a rare complication of rosacea. Generally, there are few symptomatic complaints aside from redness and facial contour changes. The edema typically worsens slowly over months to years and is often on a background of chronic inflammation. There are no specific laboratory findings associated with this condition, and the histology tends to be similar to that seen in rosacea. The differential diagnosis includes acne vulgaris, streptococcal cellulitis, and Melkersson–Rosenthal syndrome, as these conditions can also rarely manifest with a similar edema, as well as other forms of rosacea, lupus erythematosus, and sarcoidosis.

Most cases of this condition tend to be recalcitrant to treatment, with topical and oral antibiotic regiments commonly used for rosacea generally being ineffective. For the severe forms of this disease, oral isotretinoin therapy has been used, and the condition responds well to doses of 0.5 to 1 mg/kg/day. However, unlike in the treatment of acne vulgaris, lasting responses to isotretinoin generally do not occur, and long-term maintenance therapy with oral tetracyclines is usually necessary. Eyelid reduction surgery has also been reported to help with the cosmetic appearance of the condition, but does not alter the disease progression.

Essential Lessons:

- Persistent edema of rosacea is an uncommon cutaneous condition often recalcitrant to treatment.
- These cases may be treated with oral isotretinoin followed with oral tetracycline maintenance therapy.

References:

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Case #11

Case Presented by Joanne Montgomery, MD,
Aleksander Krunic, MD, PhD, and Michelle Bain, MD

History of Present Illness:
This 19 month old female presented with a rough patch on her left thigh. Her mother reports first noticing this when the patient was 4 or 5 months old and felt that it had been growing. There was no itching, pain, or other associated symptoms.

Past Medical and Surgical History:
Born full-term via Cesarean section secondary to breech presentation, presacral teratoma status post excision in December 2009, sickle shaped sacrum noted on MRI

Medications:
None

Family History:
The patient's mother has two uteri and two cervices. She had one spontaneous abortion in the past and also has a history of anal stenosis as a young child. The patient's maternal aunt has a history of presacral teratoma removed at age 12. This aunt also reportedly has two vaginas, two uteri, and two cervices. The remainder of the family history was negative for other birth defects or known genetic disorders. The parents are non-consanguineous. The patient has one younger brother who is healthy with no known sacral or urogenital malformations.

Review of Systems:
The patient has no history of seizures or constipation. She is healthy with normal growth and development.

Physical Examination:
There are multiple approximately 2 mm flesh-colored papules coalescent into an irregularly shaped pebbly plaque on the left lateral upper leg. A well-healed scar was noted at the level of the sacrum. There are no other skin findings, including no hypopigmented lesions.

Diagnostic Procedures and Tests:
Bone survey: Grossly normal. No osteolytic/osteosclerotic lesions are seen in the skull or extremities.

Echocardiogram: Normal cardiac and great vessel anatomy. Normal left ventricular systolic function.

Renal ultrasound: Within normal limits

Histopathology:
Left thigh, skin: Multiple sections show a thickened dermis with increased amount of collagen bundles in a haphazard arrangement. There is no increased dermal inflammation. The epidermis is unremarkable.

Diagnosis:
Collagenoma in the setting of Currarino syndrome

Treatment and Course:
The patient was seen by the department of Pediatric Genetics. Based on her history of presacral teratoma and bony sacral abnormality, in conjunction with her family history of presacral teratoma and urogenital abnormalities, the patient was diagnosed with Currarino syndrome. To date, there are no reported associations with connective tissue nevi and this syndrome.

Discussion:

Currarino syndrome is characterized by a triad of anorectal malformation, presacral mass, and a sacral bony defect. In affected patients, abnormal fusion of the endoderm and ectoderm in early fetal life results in failure of mesodermal fusion around the notocord. Subsequent failure of the anterior vertebrae to fuse creates an abnormal connection between the spinal column and the gut. Combination of mesodermal tissue with enteric and neuroectodermal elements leads to presacral teratoma formation. Teratoma and anterior meningocele are the two most frequent types of presacral masses in this syndrome. Other reported pathologies include lipoma, lipomeningocele, leiomyosarcoma, dermoid cyst, enteric cyst, and epidermoid cyst. The sacral bony defects range from total sacral agenesis to partial asymmetric sacral deformity. The most common anorectal malformation is anorectal stenosis.

Currarino syndrome is an autosomal dominant disorder with highly variable expressivity. The gene defect has been localized to 7q36 and is thought to involve the HLXB9 homeobox gene. The triad may be complete if all three anomalies are present or incomplete in patients with only one or two defects. The most common presenting symptom is chronic constipation, although patients may be asymptomatic.

Connective tissue nevi are hamartomatous growths of dermal connective tissue which present as solitary or multiple asymptomatic papules, nodules, or plaques. They typically arise at birth or in childhood and may be subdivided based on whether collagen, elastic fibers, or proteoglycans are involved. Histopathologic examination of a collagenoma reveals a poorly demarcated area of increased collagen fibers in a haphazard array without discernibly increased fibroblasts.

Collagenomas can be classified based on whether they are inherited or acquired. Familial cutaneous collagenoma syndrome is an autosomal dominant disorder characterized by dermal nodules on the trunk and upper extremities. This syndrome may be associated with cardiac abnormalities including idiopathic progressive myocardiopathy or electrocardiogram changes. Tuberous sclerosis, an autosomal dominant disorder with highly variable expressivity, is characterized by mental retardation, seizures, and specific skin lesions. The shagreen patch is a collagenoma which is highly characteristic of this disorder. Other genetic syndromes associated with collagenomas include multiple endocrine neoplasia type I, Birt-Hogg-Dubé syndrome, Cowden syndrome, and Proteus syndrome.

Acquired collagenomas occur in patients without a family history of connective tissue nevi. They can be either eruptive or isolated. Eruptive collagenomas affect the trunk and upper extremities similar to familial cutaneous collagenoma syndrome. Isolated collagenomas, known as paving stone nevi, do not follow this distribution. Patients with isolated collagenomas should undergo careful examination to exclude other syndromes associated with connective tissue nevi.

Essential Lessons:

- Currarino syndrome is characterized by a triad of anorectal malformation, presacral mass, and a sacral bony defect.
- Patients with isolated collagenomas should be evaluated for associated syndromes.

References:

1. Emans PJ, et al. The Currarino triad: the variable expression. *J Pediatr Surg* 2005;40(8):1238-42.
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5. Xia U and Darling TN. Rapidly growing collagenomas in multiple endocrine neoplasia type I. *J Am Acad Dermatol*;56(5):877-880.

Case # 12

Case Presented by Shruthi Reddy, MD
and Sophie Marie Worobec, MD

History of Present Illness:
This 72 year old woman presented with a long history of occasionally painful bumps on both hands with the development of multiple similar lesions on her forearms over the last six months. Past treatment included intralesional triamcinolone injections when limited lesions were present with resolution in three weeks. She also tried numerous unknown topical medications with no improvement.

Past Medical and Surgical History:
Arthrogyposis (nonprogressive condition characterized by multiple joint contractures found throughout the body at birth), multiple surgeries on her knees, neck, and back with the insertion of metal plates, neuropathy around waist and feet, osteoporosis, and osteoarthritis

Medications:
Trazodone, oxycodone, isoproterenol, gabapentin, polyethylene glycol, aspirin, calcium, multivitamin, venlafaxine, zoledronic acid

Allergies:
Sulfa

Review of Systems:
The patient reports myalgias and occasional arthralgias in her knees. She denies any weight loss.

Physical Examination:
Weight: 77 pounds
There are multiple pink to flesh-colored firm nodules over the bilateral dorsal hands, metacarpophalangeal joints, proximal fingers, and linearly along the ulnar bones. Ulnar deviation and joint contractures of both hands are noted.

Histopathology:
Right forearm, skin: Section shows a dermal nodular infiltrate of palisading histiocytes surrounding eosinophilic degenerated collagen. Colloidal iron stain highlights an increased amount of interstitial mucin.

Labs:
The following were negative or within normal limits:
Rheumatoid factor and complete metabolic panel

Diagnosis:
Multiple granuloma annulare nodules

Treatment and Course:
The patient was started on a combination course of once monthly rifampin 600 mg, ofloxacin 400 mg, and minocycline hydrochloride 100 mg. Despite completion of four months of therapy, she continued to develop new nodules.

Discussion:
Granuloma annulare (GA) is a benign, inflammatory dermatosis with several variants including limited, disseminated, perforating, and deep or pseudorheumatoid. The deep or pseudorheumatoid nodular form typically presents with nodules in the subcutis, which may occur near the knees, ankles, elbows, or the small joints of the hands. The clinical distinction between this form of GA and rheumatoid nodules can

be difficult. However, the subcutaneous nodules of rheumatoid arthritis tend to occur during the active phase of the disease in individuals with a circulating rheumatoid factor. The pathogenesis of GA is thought to represent a delayed-type hypersensitivity reaction to an unknown antigen characterized by a predominantly CD4+ lymphocytic TH-1 inflammatory response. It is postulated that increased levels of interleukin-2, interferon-γ, and tumor-necrosis factor-α stimulate macrophages and recruit T-lymphocytes which amplify the inflammatory response while metalloproteinases degrade collagen and other matrix proteins.

Histologically, GA is characterized by foci of degenerative collagen surrounded by palisading granulomas in the superficial and deep dermis. Abundant mucin is the hallmark. The palisading granulomas of rheumatoid nodules are in the deep dermis and subcutis with increased fibrinoid degeneration of collagen. In contrast, increased histiocytes and mucin deposits, absent or scant deposits of fibrin, and less stromal fibrosis are typically seen in the nodular form of GA. Recent studies have shown that GA, sarcoid granulomas, and necrobiosis lipoidica diabeticorum lesions stain highly positive for glioma oncogene homologue (gli)-1, one of the vertebrate zinc finger genes of the gli superfamily, which may have implications for treatment in the future.

GA, especially the localized variant, often resolves spontaneously. However, many therapies have been reported to be effective including high-potency topical steroids, cryotherapy, or intralesional corticosteroid injections. Unfortunately, these therapies are inadequate for multi-nodular or disseminated GA where many areas of the body require treatment. In the nodular variant, persistence, recurrence, and appearance of new lesions are generally the rule with intralesional corticosteroid injections being the most effective treatment. Clinical and histological similarities between GA and leprosy have led some to attempt treatment of GA with antibiotic regimens used to treat leprosy. Because of the known anti-inflammatory effects of tetracyclines and the reported safety profile of monthly triple rifampin, ofloxacin, and minocycline (ROM) combination therapy, ROM therapy was tried and proved to be effective and safe in six cases of resistant GA treated at Henry Ford Hospital. Alternatively, the finding of gli-1 staining provides a rationale for clinical trials of inhibitors of gli-1 signaling such as tacrolimus and sirolimus for the therapy of granulomatous skin disorders including severe cases of GA.

Essential Lessons:

- Granuloma annulare nodules may mimic rheumatoid arthritis clinically but can be differentiated histologically.
- No single therapeutic intervention is considered the treatment of choice.

References:

1. Barzilai A, et al. Pseudorheumatoid nodules in adults: a juxta-articular form of nodular granuloma annulare. *Am J Dermatopathol* 2005;27(1):1-5.
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6. Raghava N, et al. Granuloma annulare presenting as multiple nodules on the pinna. *J Laryngol Otol* 2004;118(8):640-2.

Case # 13

Case Presented by Carmen Schwartz, MD
and Lawrence Chan, MD

History of Present Illness:
This 43 year old male presented for evaluation of a changing birthmark on his left leg. The birthmark was initially flat and smooth, but it had become thicker over the past 20 years. New, painful growths within the birthmark developed over the last several months.

Past Medical and Surgical History:
Obstructive sleep apnea, borderline hypertension

Medications:
Docusate

Allergies:
No known drug allergies

Review of Systems:
He denied fevers, chills, nausea, vomiting, or joint pains.

Physical Examination:
Over the left leg, extending from the distal thigh to the distal lateral one-third of the shin following Blaschko's lines is a linear, cobblestone to verrucous, dark brown plaque. Within the plaque on the left popliteal fossa are several 1 cm verrucous, hyperkeratotic plaques. Near the distal border of the verrucous plaque in the left central popliteal fossa is a 4 mm erythematous, scaly, round papule.

Laboratory Data/Diagnostic Procedures and Tests:
None

Histopathology:
Left lower calf, skin: Multiple sections show papillomatous epidermal hyperplasia with hyperpigmentation of basal layer keratinocytes. There is no significant dermal infiltrate.

Left central popliteal fossa, skin: Multiple sections show papillomatous epidermal hyperplasia. There is also prominent apocrine hyperplasia in the underlying dermis. Multiple foci of basaloid nests are identified, some of which are pigmented. In one focus, there are papillary projections protruding into the invaginations of surface epithelium. A lymphoplasmacytic infiltrate is identified in the surrounding stroma.

Left popliteal fossa, superior and inferior, skin: Section shows exoendophytic proliferation of well-differentiated keratinocytes with increased hyperkeratosis and parakeratosis. The keratinocytes display a degree of cytologic atypia with scattered dyskeratosis. At the base of the lesion, there is a mixed inflammatory infiltrate with lymphocytes and eosinophils. There is no evidence of infiltrative growth pattern.

Diagnosis:
Syringocystadenoma papilliferum and keratoacanthomas arising in an epidermal nevus

Treatment and Course:
The patient underwent shave removal of the tumors with no recurrence over the last year. He continues to be followed closely in dermatology.

Discussion:

Epidermal nevi are benign cutaneous hamartomas typically noted at birth or within the first year of life as a linear tan patch or thin plaque often following Blaschko's lines. Rarely epidermal nevi develop in late childhood. Around the time of puberty, epidermal nevi become thicker, more verrucous, and hyperpigmented. Epidermal nevi have a predilection for the trunk and extremities. Rarely, keratinocytic or adnexal neoplasms may occur warranting a biopsy of any new appearing lesion within a stable epidermal nevus.

Syringocystadenoma papilliferum (SCAP) is an uncommon benign adnexal neoplasm with varying clinical appearances. The majority of SCAP develop on the head and neck as a warty plaque, often occurring in association with nevus sebaceous. Other uncommon anatomic locations for SCAP include the trunk, extremities, breast, buttock, and inguinal areas. Most develop as solitary lesions, but rare clinical patterns including linear and segmental variants have been described.

Despite the clinical diversity of SCAP, its histology is distinctive with duct-like invaginations and cyst-like cavities of varying shapes and sizes extending from the epidermal surface into the body of the lesion. The invaginations are lined by bilayered epithelium composed of both a basilar cuboidal row of cells and an apical columnar row. A chronic plasmalymphocytic inflammatory infiltrate is found in the stroma surrounding these duct-like structures.

Keratoacanthomas (KA) usually occur spontaneously as a single rapidly growing tumor in sun-exposed areas. They appear as firm, dome-shaped papules or nodules with a central keratin plug. Characteristically, KAs have a rapid growth phase, followed by a stationary period, and finally undergo spontaneous involution, healing as a slightly depressed scar. The most frequent clinical and histological consideration in the differential diagnosis of a KA is that of squamous cell carcinoma. Histologically, KAs display a keratin-filled crater lined by a proliferating squamous epithelium and prominent keratinization of the squamous cells producing a glassy appearance. Cytological atypia is absent to mild and mitotic figures are rare in KA. There have been rare case reports of keratocanthomas arising within epidermal nevi.

Essential Lessons:

- Syringocystadenoma papilliferum and keratoacanthoma are both rare tumors found to develop within epidermal nevi.
- Any new growth within a stable epidermal nevus should be biopsied to rule out a neoplasm.

References:

1. Brandling-Bennett HA, Morel KD. Epidermal nevi. *Pediatr Clin North Am* 2010;57(5):1177-98.
2. Braunstein BL, et al. Keratoacanthomas arising in a linear epidermal nevus. *Arch Dermatol* 1982;118(5):362-3.
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Case # 14

Case Presented by Amanda Cooper, MD
and Iris Aronson, MD

History of Present Illness:
This 50 year old female with a history of systemic sclerosis presented with an asymptomatic rash on her distal fingers and scalp. The rash began three months prior after discontinuation of methotrexate. The methotrexate was recently restarted and the skin lesions have improved, but not cleared. She also noted solitary plaques on her abdomen and buttock that had waxed and waned over the past year.

Past Medical and Surgical History:
Scleroderma diagnosed in 1996 (esophageal abnormalities on endoscopy, calcinosis cutis with digital ulcerations, sclerodactyly, Raynaud's phenomenon); endometrial ablation

Medications:
Methotrexate, esomeprazole, pentoxifylline, and folic acid

Allergies:
No known drug allergies

Family History:
Great aunt with systemic sclerosis. No family history of skin cancer.

Social History:
The patient denies smoking, alcohol, or drug use. She is married with three children.

Review of Systems:
She reports weakness when holding her arms above her head and shortness of breath on exertion.

Physical Examination:
There is diffuse scaling and erythema of the scalp. There is tightness of her facial skin with an oral aperture of 3 fingerbreadths. Her hands show loss of finger fat pads, sclerodactyly with reduced flexion of fingers, and violaceous thin plaques over her joints. Cuticles are without dilated capillary loops. On her right abdomen is a 1.4 cm x 0.8 cm erythematous, atrophic plaque. On her left medial buttock is a 4 mm erythematous, hyperkeratotic papule.

Laboratory Data:
The following were positive or abnormal:
Creatine kinase 303 u/L (20-185), thyroid stimulating hormone 5.5 mIU/mL (0.35-4), erythrocyte sedimentation rate 39 mm/hr (0-20), antinuclear antibody titer 1:320, speckled pattern

The following were normal or negative:
Complete metabolic panel, antibodies to centromere, Scl-70, RNP, Smith, SSA, SSB, double stranded DNA, and cardiolipin

Diagnostic Procedures and Tests:
Pulmonary function tests and echocardiogram: normal

Histopathology:
Right abdomen and left medial buttock, skin: Both biopsies show similar changes. Sections show superficial and deep perivascular and periadnexal infiltrate of lymphocytes and plasma cells. This is associated with interface dermatitis with basal layer vacuolar changes. In the deep dermis, there is thickened collagen bundles focally replacing periadnexal adipose tissue. PAS stain highlights the thickened basement membrane without evidence of fungal elements.

Diagnosis:
Overlap systemic sclerosis and dermatomyositis

Treatment and Course:
The patient continued methotrexate and lesions continue to improve. She reports near resolution of lesions with use of calcipotriene 0.005%/betamethasone dipropionate 0.064% ointment.

Discussion:
Systemic sclerosis (SSc) is a connective tissue disease that is characterized by vascular injury and fibrosis affecting the skin, blood vessels, and organs including the lungs, kidneys, heart, and gastrointestinal tract. As with many of the connective tissue diseases, SSc can overlap with other connective tissue diseases in the same patient. Dermatomyositis (DM) has been reported in overlap syndromes with SSc. DM is characterized by an inflammatory myopathy of proximal muscles and a cutaneous eruption including photodistributed poikiloderma and violaceous discoloration over the knuckles (Gottron's sign) and periocular area (heliotrope sign). When the violaceous patches over the knuckles become lichenoid, they are known as Gottron's papules.

SSc patients with diffuse cutaneous involvement have been found to express the following autoantibodies: Scl-70 (60%), centromere (30%), Fibrillin-1 (5%), Th/To RNP (11%) and HMG (30%). Overlap syndromes of SSc with DM are associated with different serology profile. The most common autoantibody is against an exosome complex component, anti-PM Scl, which is present in approximately 24% of these overlap cases. Other antibodies reported in SSc/DM overlap include anti-Ku and anti-U2RNP.

Essential Lessons:
- Consider overlap syndromes when atypical presentations of connective tissue diseases occur.
- Systemic sclerosis/dermatomyositis overlap is associated with anti-PM Scl, anti-Ku, and anti-U2RNP antibodies.

References:

1. Gutiérrez-Ramos R, et al. A dermatomyositis and scleroderma overlap syndrome with a remarkable high titer of anti-exosome antibodies. *Reumatismo* 2008;60(4):296-300.
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Case # 15

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

History of Present Illness:
The patient is a 28 year old white female who presented one year ago with linear scleroderma diagnosed in 2004. Initially only her right forehead was involved, but she had gradual spreading to her scalp and posterior neck. Right eye involvement manifested with strabismus, lid retraction, and exposure keratopathy in 2007. On presentation, treatment included topical calcipotriene solution, betamethasone dipropionate cream, cyclosporine 200 mg daily, and hydroxychloroquine 200 mg twice daily. Disease progression had slowed with this regimen.

Past Medical and Surgical History:
Attention deficit disorder, acne vulgaris

Medications:
Cyclosporine, hydroxychloroquine, calcipotriene solution, betamethasone dipropionate cream, lubricant eye drops; ethinyl estradiol-norgestimate oral contraceptive; adapalene 0.1% gel and doxycycline for acne vulgaris; fluocinolone/hydroquinone/tretinoin cream for neck hyperpigmentation

Allergies:
No known drug allergies

Family History:
Negative for skin diseases

Review of systems:
The patient experienced diplopia and painful right eye xerophthalmia. She suffered from right neck spasms. A complete review of systems was otherwise negative.

Physical Examination:
There is an atrophic, depressed, indurated, linear plaque extending from the right oral commissure to the right nasal ala and sidewall. There is medial conjunctival injection and atrophy of the right medial upper eyelid. The indurated plaque extends superiorly, widens at the forehead, and continues onto the right frontal scalp in a linear fashion. There is associated scarring alopecia. The right posterior neck has a large, poikilodermatous, slightly atrophic plaque.

Laboratory Data:
The following were negative or within normal limits:
Complete blood count, complete metabolic panel, antinuclear antibody, anti-Scl 70 antibody, anti-ribonucleoprotein antibody, anti-Smith antibody, anti-Ro antibody, anti-La antibody, lactate dehydrogenase

Diagnostic Procedures and Tests:
The following were within normal limits:
Echocardiogram, pulmonary function tests, chest radiograph

Diagnosis:
Linear scleroderma, *en coup de sabre* type

Treatment and Course:
The patient remains on her regimen of cyclosporine, hydroxychloroquine, calcipotriene solution, and betamethasone dipropionate cream. She underwent surgical correction of her right upper eyelid retraction. Despite a recent two month lapse in systemic treatment, her disease is stable without progression.

Discussion:
Morphea, or localized scleroderma, is an uncommon skin disorder characterized by skin thickening and fibrosis. It may involve deeper structures, but there is no systemic involvement. Its etiology is unknown although hypothesized to be autoimmune in nature. Clinically, lesions are initially erythematous and progress to yellow-white plaques with lilac borders. The affected skin becomes atrophic, alopecic, and dyschromic. Based on clinical findings, morphea is classified into plaque, generalized, bullous, deep, and linear types.

Linear scleroderma (LS) is a variant characterized by longitudinal bands of sclerosis. This type of morphea most commonly affects young adults and children with an average onset at 18 years. Typical locations for LS are the extremities and face. LS may extend deeply into tissues affecting muscle and bone. Arthritis, synovitis, and joint contractures are thus potential complications. When the paramedian forehead or fronto-parietal scalp are involved, the clinical term *en coup de sabre* (ECDS) is used. This LS subtype has unique potential complications involving the central nervous system (CNS), eyes, and teeth. Headache, focal neurological deficits, seizures, or hemiparesis can occur. CNS imaging studies can show cortical calcification or atrophy, and cerebral spinal fluid can contain inflammatory cells. Ocular findings include eyelid abnormalities, refractive errors, strabismus, episcleritis, uveitis, pseudopapilledema, and vasculitis. Dental abnormalities and mandibular misalignment can also occur.

Halting the inflammatory phase of morphea, thus preventing long-term sequelae, is the treatment goal. Topical, intralesional, and systemic glucocorticoids are often used as first-line therapy. Phototherapy and photochemotherapy can also be effective. UVA alone or with topical psoralens may be used to treat active morphea. UVA1 is superior in treating fibrosis. Methotrexate has been used alone or in combination with glucocorticoids with good results. Other treatment modalities include topical and oral vitamin D analogs, acitretin, antimalarials, mycophenolate mofetil, cyclosporine, imiquimod, topical tacrolimus, photodynamic therapy, and pulsed dye laser. Treatment modalities with more sporadic or marginal efficacy include colchicine, penicillin, D-penicillamine, and phenytoin. Physical therapy may be indicated to prevent contractures and permanent disability in cases of LS.

When active inflammation ceases, treatment should be altered to address atrophy and sclerosis. Physiotherapy and emollients may be helpful. For permanent contractures, surgery should be considered. ECDS patients may have improved cosmesis with various surgical and reconstructive procedures; however, it is important to postpone surgery until the disease is inactive for six to twelve months.

Essential Lesson:
- *En coup de sabre* is a type of facial linear scleroderma. It may extend deeply to involve muscle, bone, teeth, eyes, and central nervous system.

References:

1. Martini G, et al. Successful treatment of severe or methotrexate-resistant juvenile localized scleroderma with mycophenolate mofetil. *Rheumatology* (Oxford). 2009 Nov;48(11):1410-3.
2. Vilela FA, et al. Treatment of morphea or localized scleroderma: review of the literature. *J Drugs Dermatol* 2010 Oct;9(10):1213-9.
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Case # 16

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

History of Present Illness:
This 44 year old female presented with chronic itching and new onset blistering. For three years, she had itching of her scalp, back, arms and upper chest. At times she developed itchy bumps on her arms and she admitted to picking at these lesions, when anxious. Over the past three months, she developed blisters on the arms and hands, and she experienced a burning sensation when they ruptured. She described herself as an avid sun-bather.

Past Medical and Surgical History:
Hepatitis C, history of liver biopsy in 2004, eczema, asthma, endometriosis, bipolar disorder, macrocytosis

Medications:
Quetiapine fumarate, zolpidem tartrate, ziprasidone, ropinirole hydrochloride, albuterol sulfate inhaler, hydrocodone bitartrate and acetaminophen

Allergies:
Tramadol hydrochloride

Family History:
Daughter with eczema, mother with lung cancer and diabetes mellitus, no inherited blistering disorders

Social History:
She is a prior alcoholic, but has been sober for 1.5 years. She has a 20 pack year history of smoking. She denied a history of intravenous drug abuse.

Review of Systems:
The patient noted occasional shortness of breath along with chronic joint pains and body aches, otherwise the review of systems was negative.

Physical Examination:
There is a single excoriation on the vertex scalp and the left forehead. Diffusely over the lateral forehead, cheeks and chin bilaterally is an increased density of blond terminal hairs. Scattered over the dorsal surfaces of the upper arms, forearms and hands are many erythematous erosions with hemorrhagic crusting and pink to hypopigmented atrophic macules. On the right thumb and left middle finger are clear, fluid-filled, tense bullae.

Laboratory Data/Diagnostic Procedures and Tests:
The following were positive or abnormal:
Urine uroporphyrin 73 µmol/mol creatinine (0-4), heptacarboxylporphyrin 116 µmol/mol creatinine (0-2), coproporphyrin I 8 µmol/mol creatinine (0-6), coproporphyrin III 22 µmol/mol creatinine (0-14), ferritin 319 ng/mL (5-116), mean corpuscular volume 113.7 fl (80-99), mean corpuscular hemoglobin 37.7 pg (26-35), platelet 500 k/µl (150-450), total hemolytic complement (CH50) 55 CAE units (60-144)

The following were negative or within normal limits:
Antinuclear antibody, iron, folate, vitamin B12, hemoglobin, basic metabolic panel, liver function tests

Histopathology/Immunopathology:
H&E, left middle finger, lesional skin: Sections show subepidermal vesiculation with festooning of dermal papillae. There is no significant inflammatory infiltrate. There is a hyalinized appearance in the superficial dermal small blood vessels. A few dyskeratotic keratinocytes are also identified. A small amount of eosinophilic basement membrane material is present in the epidermis. Basement membrane material surrounding blood vessels and along the basal layer of the epidermis is highlighted with the PAS stain.

Direct immunofluorescence, left forearm, perilesional skin: There is strong deposition of IgG, IgM, and IgA around thickened dermal blood vessels. There is non-specific staining of IgG against the thickened basement membrane.

Diagnosis:
Porphyria cutanea tarda

Treatment and Course:
The patient was started on therapeutic phlebotomy of 500 mL weekly to obtain a hemoglobin level of 11g/dL. We recommended strict sun protection with physical barrier sunscreens and protective clothing, along with continued avoidance of estrogen containing medications and alcohol. Referral was made to Hepatology for treatment options of her chronic hepatitis C.

Discussion:
Porphyria cutanea tarda (PCT) is caused by enzymatic deficiency of uroporphyrinogen decarboxylase (UPD), the fifth enzyme in the heme synthesis pathway. The acquired or sporadic form of PCT, which makes up approximately 75% of cases, is characterized by hepatocyte enzyme deficiency caused by exogenous injury. Clinical findings include skin fragility with blistering, crusted erosions, milia, and scarring in photodistributed areas. Hypertrichosis, postinflammatory dyspigmentation, scarring alopecia, and sclerodermoid changes can also be found.

PCT triggers include alcohol, estrogens, chloroquine, viral infections such as hepatitis C and HIV, polychlorinated hydrocarbons, hemodialysis, and hemochromatosis. The exact role of alcohol and hepatitis C infection in PCT is not fully understood. One proposed mechanism is stimulated release of iron from ferritin storage that subsequently generates free radicals. The resultant free radicals might directly inhibit the sulfhydryl groups of the enzyme UPD. Alternatively, free radicals could indirectly convert porphyrinogen substrates into non-metabolizable porphyrins, which then accumulate.

Treatment of PCT includes avoidance of precipitating factors. Medical therapy is aimed at reducing iron overload by phlebotomy, erythropoietin, or deferoxamine. Additionally, antimalarials, thalidomide, and plasma exchange can reduce accumulated porphyrins. Treatment of associated hepatitis C with interferon or ribavirin can be helpful. Case reports have described cimetidine and oral antioxidants as additional PCT treatment options.

Essential Lessons:
- Porphyria cutanea tarda is an acquired deficiency of the heme enzyme uroporphyrinogen decarboxylase
- Therapeutic phlebotomy to reduce iron stores and strict sun protection can reduce skin manifestations

References:

1. Doss MO, et al. Alcohol and porphyrin metabolism. *Alcohol* 2000;35(2):109-25.
2. Rebora A. Skin diseases associated with hepatitis C virus: facts and controversies. *Clin Dermatol* 2010;28(5): 489-96.
3. Sarkany RP. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001;26(3):225-32.
4. Thadani H, et al. Diagnosis and management of porphyria. *BMJ* 2000;320(7250):1647-51.

Case # 17

Case Presented by Karl Vance, MD
and Michelle Bain, MD

History of Present Illness:
This 5 month old Hispanic female was evaluated at 3 weeks of age with a newly noted erythematous patch on the occipital scalp. She was born prematurely at 37 weeks due to intrauterine growth restriction and had undergone extensive workup for multiple congenital abnormalities.

Past Medical and Surgical History:
Failed newborn hearing screen with persistent, severe, bilateral hearing loss, gastrostomy tube placed for poor oral intake, small secundum atrialseptal defect, patent ductus arteriosus, soft palate cleft, nasolacrimal duct obstruction, left dacryocystitis, left hydronephrosis

Medications:
Ranitidine

Allergies:
No known drug allergies

Family History:
Non-contributory; no known history of Cornelia de Lange syndrome

Review of Systems:
Mother reports occasional diarrhea. Denies fevers, chills, vomiting, cough, runny nose, or lethargy.

Physical Examination:
Head circumference, body weight, and length are all under the third percentile. She has a weak cry diffuse hypertrichosis with synophrys, long eyelashes, and a low posterior hair line. Long, flat philtrum with thin upper lip, retrognathia, and low set ears with narrow ear canals are noted. Persistent cutis marmorata is noted on the chest and abdomen. There are flexion contractures in her bilateral elbows and camptodactyly of bilateral middle fingers. Over the posterior scalp, near the vertex, is a 1.5 cm bright red, smooth, membranous, hairless plaque.

Laboratory Data:
The following were positive or abnormal:
Mutation in the *NIPBL* gene (c. 1576C->T; p. Q526X), hemoglobin 10.7 g/dL (14.5-24.5)

The following were negative or within normal limits:
Basic metabolic panel

Radiology:
Computed tomography, head: no acute intracranial or bony abnormality

Diagnosis:
Cornelia de Lange Syndrome with aplasia cutis congenita

Treatment and Course:
At follow up, the scalp lesion remains unchanged.

Discussion:

Cornelia de Lange syndrome (CdLS) is a rare, genetically heterogeneous, multiple malformation disorder, characterized by small stature, developmental delay, distinctive facial features, hearing loss, and occasional major malformations. The prevalence is estimated at 1:10,000, though this may be artificially low as phenotypically milder cases are likely underreported. Nearly all cases (99%) are spontaneous and dominant and the vast majority of affected individuals have a de novo mutation. Recurrence in siblings due to parental mosaicism has been reported.

Mutations in three cohesion proteins account for approximately 65% of cases. The cohesion complex is responsible for sister chromatid segregation during mitosis and meiosis and is also involved in DNA repair. NIPBL, a key regulator of cohesion, is mutated in approximately 50% of cases, while the structural components of the cohesion ring, SMC1A and SMC3, are mutated in the other 15%.

The diagnosis of CdLS is made clinically. Minimal diagnostic criteria and a severity assessment scale have recently been published. When biological testing reveals a mutation in one of the associated genes, the patient will also, by definition, have CdLS. Clinically, patients should meet facial criteria and criteria for two of six other systems. Craniofacial features include synophrys, arched eyebrows, long eyelashes, small upturned nose, long philtrum, thin upper lip, micrognathia, and microcephaly. Other systems affected include growth, development, behavior, musculoskeletal, neurosensory/skin, and other. Additional cutaneous manifestations include cutis marmorata and hypoplastic nipples, umbilicus, and genitalia.

Aplasia cutis congenita is a rare, congenital defect of the skin characterized by absence of the epidermis, dermis, and occasionally subcutaneous tissues. It clinically presents as a solitary, sharply demarcated ulceration or erosion which heals leaving a smooth, hairless scar. The scalp, near the vertex, is the most common site of involvement, though lesions may appear anywhere. The lesions are most often sporadic and isolated, though they may be associated with underlying encephalocele, cleft lip or palate, limb reduction defects, epidermolysis bullosa, specific teratogens, intrauterine infections, or other embryologic malformations.

Essential Lessons:

- CdLS is a rare, heterogeneous, multiple malformation syndrome with characteristic craniofacial findings as well as multiple other system involvement.
- The vast majority of cases are sporadic dominant: mutations in NIPBL, SMC1A and SMC3, all components of the cohesion complex, account for approximately 65% of cases.
- Aplasia cutis congenita has not been reported as part of CdLS, though it can be seen with other embryologic malformations.

References:

1. Frieden I. Aplasia cutis congenita: a clinical review and proposal for classification. *J Am Acad Dermatol* 1986;14:646-60.
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Case #18

Case Presented by Brendan Thomas, MD
and Milena Lyon, MD

History of Present Illness:
This 28 year old male presented in early 2010 with an approximately four month history of a painless, enlarging mass on the right upper arm. During the same time, the patient also noticed a new, slowly enlarging growth on the right cheek and a purple discoloration on the tip of the nose. The patient has a seven year history of human immunodeficiency virus (HIV) and had been on highly active antiretroviral therapy (HAART) years prior. He restarted HAART one month prior to presentation.

Past Medical and Surgical History:
HIV positive for seven years

Medications:
Didanosine, lamivudine/abacavir, ritonavir

Allergies:
No known drug allergies

Family History:
No history of skin cancer or other skin conditions

Social History:
The patient uses occasional tobacco and alcohol. He denies illicit drug use.

Physical Examination:
Examination revealed a thin man in no obvious distress. On the nose were several scattered, well demarcated, thin, violaceous plaques. Over the right inferior malar surface/jawline was an erythematous, eroded papule. The right upper arm had a chain of six violaceous, smooth papules, adjacent to a 3 cm erythematous, friable mass, draining serous fluid. Throughout the upper and lower extremities were approximately 30 small, erythematous to violaceous patches and thin plaques. He had a violaceous nodule on the left anterior thigh. Anterior and posterior cervical lymphadenopathy was appreciated.

Laboratory Data:
The following were positive or abnormal:
CD4 count <200 cells/μL

Histopathology:
Left nasal bridge and left anterior thigh, skin: Both biopsies demonstrate proliferation of poorly formed blood vessels lined by plump spindle cells. Slit-like spaces are easy to identify. There is background inflammatory infiltrate containing plasma cells and lymphocytes. Hemosiderin deposition is also present. The plump spindle cells and slit-like spaces are highlighted by CD31 staining. The human herpesvirus 8 (HHV-8) stain is positive in both specimens.

Diagnosis:
AIDS-related Kaposi's sarcoma

Treatment and Course:

After the initial biopsies confirmed the diagnosis of Kaposi's sarcoma, two additional lesions were surgically excised from the right upper arm and right jawline due to their size and cosmetic appearance. This histology was also consistent with Kaposi's sarcoma. The patient was repeatedly encouraged to follow-up with his infectious disease physician, continue HAART, and have imaging performed to rule out internal involvement; however, the patient was lost to follow-up.

Discussion:

Kaposi's sarcoma (KS) is a systemic disease which can present with cutaneous lesions with or without internal involvement. Four subtypes have been described: Classic KS, affecting middle aged men of Mediterranean and Jewish descent, African endemic KS, KS in iatrogenically immunosuppressed patients, and AIDS-related KS. The erythematous to violaceous cutaneous lesions seen in KS have several morphologies: macular, patch, plaque, nodular, and exophytic. The cutaneous lesions can be solitary, localized or disseminated. KS can involve the oral cavity, lymph nodes, and viscera. The pathogenesis of KS is still being elucidated, though infection with HHV-8 appears to be associated with KS development. Classic KS tends to be indolent, presenting with erythematous or violaceous patches on the lower extremities. African endemic KS and AIDS-related KS tend to be more aggressive. The AIDS-related KS lesions often rapidly progress to plaques and nodules affecting the upper truck, face, and oral mucosa. The diagnosis can be made with a tissue biopsy and, if clinically indicated, internal imaging should be done.

Once the diagnosis of KS has been made, treatment is based on the subtype and the presence of localized versus systemic disease. Localized cutaneous disease can be treated with cryotherapy, intralesional injections of vinblastine, alitretinoin gel, radiotherapy, topical immunotherapy (imiquimod), or surgical excision. Extensive cutaneous disease and/or internal disease may require IV chemotherapy and immunotherapy. Discontinuation or reduction of immunosuppressive therapy is recommended when KS arises in the setting of iatrogenic immunosuppression. However, with AIDS-related KS, HAART has been shown to prevent or induce regression of KS. Some AIDS patients have complete resolution of the lesions and prolonged remission while continuing the therapy. Therefore, HAART should be considered first-line treatment for these patients, though they may require other concomitant treatments.

Essential Lesson:

- AIDS-related Kaposi's sarcoma is an aggressive disease for which HAART should be considered first-line treatment.

References:

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Case #19

Case Presented by Adrienne Schupbach, MD and Claudia Hernandez, MD

History of Present Illness:
This 23 year old female presented with the complaint of dark skin on her arms and neck for several years. She noted that multiple family members have the same dark coloration of these areas as well. She also reported redness of her face with bumps on her cheeks and increased facial hair.

Past Medical and Surgical History:
Gravida3Para1Abortus2 with two miscarriages, gestational diabetes, oligomenorrhea (last menses was four months prior to her first visit)

Medications:
None

Allergies:
No known drug allergies

Family History:
Father and both grandmothers with diabetes

Review of Systems:
The patient reported irregular menses and a weight gain of 25 pounds after the birth of her child. She denied fevers, chills, vomiting, polyuria, or polydipsia.

Physical Examination:
Over the bilateral temples extending onto the cheeks are multiple, monomorphic, erythematous papules. There is increased terminal facial hair on the upper lip and chin. The posterior neck and bilateral antecubital fossae have linear, velvety, hyperpigmented plaques. Thick dark hair is noted over the dorsal arms.

Laboratory Data:
The following were positive or abnormal:
Fasting glucose 104 mg/dL (65-99), insulin level 38 μU/mL (3-19), dehydroepiandrosterone sulfate 432 μg/dL (65-380), sex hormone binding globulin 19 nmol/L (30-135), high-density lipoprotein 33 mg/dL (40-60), aspartate aminotransferase 46 u/L (10-40), alanine aminotransferase 83 u/L (10-50)

The following were negative or within normal limits:
Hemoglobin A1c**,** low-density lipoprotein**,** total cholesterol, triglycerides, thyroid stimulating hormone, prolactin, testosterone, free testosterone

Diagnosis:
Hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome

Treatment and Course:
The patient was referred to Endocrinology for further evaluation and work up of her insulin resistance and hyperandrogenism. Initial laboratory testing was completed, but the patient failed to follow up for further testing and management. She was started on clindamycin gel twice daily to the affected areas of the face

for treatment of her acne, while treatment of her acanthosis nigricans was deferred until completion of her endocrine evaluation.

Discussion:

The hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN) syndrome is an unusual multisystem condition affecting females. Studies have estimated that 1-3% of all hyperandrogenic women have insulin resistance and acanthosis nigricans. The precipitating abnormality in HAIR-AN syndrome is thought to be insulin resistance, with subsequent increase in insulin levels. Acanthosis nigricans occurs secondary to elevated insulin levels cross reacting with receptors for insulin-like growth factors on keratinocytes or fibroblasts, leading to proliferation of the epidermis. Similarly, hyperandrogenism is thought to result from insulin binding to insulin-like growth factor receptors in the ovarian stroma stimulating androgen production. Acanthosis nigricans is associated with many diseases, including internal malignancy, specifically gastric adenocarcinoma, along with benign conditions including endocrine abnormalities. It is a well known marker for insulin resistance, and can also be seen with obesity.

Patients with HAIR-AN syndrome often have elevated insulin levels, high-normal or elevated testosterone and dehydroepiandrosterone sulfate levels, and normal prolactin and leutinizing hormone levels. Although a specific treatment regimen has not been established for patients with HAIR-AN syndrome, weight loss and antiandrogen therapy, including estrogen-progesterone oral contraceptives, spironolactone, flutamide, and finasteride, have been found to be beneficial. These patients are at increased risk for accelerated cardiovascular disease and diabetes mellitus and should be followed by appropriate medical specialists.

Essential Lessons:

- Insulin resistance is the precipitating abnormality in HAIR-AN syndrome, consisting of hyperandrogenism, insulin resistance, and acanthosis nigricans.
- Patients with HAIR-AN syndrome are at increased risk for accelerated cardiovascular disease and diabetes mellitus and should be monitored closely.

References:

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Case # 20

Case Presented by Eliana Krulig, MD,
and Milena Lyon, MD

History of Present Illness:
A 68 year old African American female presented to clinic for evaluation of facial hyperpigmentation. She noted the onset of dark spots on her cheeks and around her eyes over 20 years ago. She started using various over-the-counter bleaching creams at that time, initially experiencing improvement. After several years of use, she noted worsening of the discoloration and no further improvement with the bleaching creams. She discontinued the bleaching creams one year prior to presentation. The patient denied any history of itching or scaling.

Past Medical and Surgical History:
Hypertension, dyslipidemia, glaucoma, arthritis, tubal ligation

Medications:
Valsartan, aspirin, diltiazem, simvastatin, brinzolamide ophthalmic drops, calcium, vitamin D

Allergies:
No known drug allergies

Family History:
No family history of skin disorders

Social History:
No history of tobacco or alcohol use

Physical Examination:
On the face, there are bilaterally symmetric, speckled, blue-black patches on the periorbital skin, malar cheeks, and above the upper lip.

Histopathology:
Left temple, skin: Sections show yellow discoloration of collagen bundles, with banana-shaped fibers. There is no increased dermal inflammation or melanophages. The epidermis is unremarkable.

Diagnosis:
Exogenous ochronosis

Treatment and Course:
The patient was advised to stop all hydroquinone-containing products and use a sunscreen. She was referred for possible laser treatment.

Discussion:
Ochronosis can be divided into endogenous and exogenous forms. Endogenous ochronosis, or alkaptonuria, is an autosomal recessive disorder caused by a lack of homogentisic acid oxidase. This results in accumulation of homogentisic acid. The earliest finding is dark urine in the diaper. Later, towards the third decade, blue-black pigmentation of the cartilage is noticeable on ear helices and the nasal tip. In addition, this pigmentation can appear on the sclerae, axillae, and palmoplantar skin. Internally, arthropathy of the large joints and vertebral column occurs. Renal calculi and kidney failure have been reported.

The exogenous form of ochronosis is an acquired disorder characterized by asymptomatic, blue-black macules, located mainly over bony prominences of the face. This is most commonly a result of hydroquinone (HQ) use, but it has also been reported with resorcinol, phenol, and mercurials. There are no associated systemic findings. It is thought that HQ locally inhibits the enzyme homogentisic acid oxidase. Originally, it was believed that only high concentrations of HQ caused exogenous ochronosis. However, it appears that prolonged use of low concentration preparations can also result in this condition.

Histopathologic studies are necessary to distinguish ochronosis from other causes of facial hyperpigmentation. The differential diagnosis includes melasma, post-inflammatory hyperpigmentation, and bilateral nevus of Ota. Histologically, exogenous and endogenous ochronosis have short, yellow-brown, curvilinear (banana-shaped) bodies within the papillary dermis. Degeneration of collagen bundles can be observed. Recently, dermoscopic features of ochronosis have been described. These findings consist of irregular, brown-gray, globular, annular, and arciform structures that represent the banana-shaped fibers seen in the dermis on histology.

There is no known effective treatment for ochronosis. Discontinuation of HQ can result in mild fading of the discoloration. Topical agents, including sunscreens and retinoids, can be helpful. Dermabrasion, intense pulsed light, and CO2, Q-switched, and alexandrite lasers have been variably effective.

Essential Lesson:

- Exogenous ochronosis can be secondary to prolonged application of low concentration hydroquinone.
- Banana-shaped bodies in the upper dermis are diagnostic of ochronosis.

References:

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