Chicago Dermatological Society

October 2014
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, October 8, 2014

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** *Student Center West, 2nd floor Foyer*
9:00 a.m. - 10:00 a.m.	**Resident Lecture** – *SCW Chicago Room A-C* "Why I Chose a Career in Academics" *Rachael Clark, MD, PhD*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** Patient & Poster Viewing *Dermatology Clinic, Suite 3E* Slide Viewing *Student Center West, Room 213 A/B*
11:00 a.m. - 12:00 p.m.	**General Session** - *SCW Chicago Room A-C* FRETZIN LECTURE: "The Magic and Mayhem of Human Skin Resident T Cells" *Rachael Clark, MD, PhD*
12:00 p.m. - 12:40 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, November 5, 2014 at Northwestern University; Lawrence Eichenfield, MD; University of California - San Diego

Watch for details on the CDS website: www.ChicagoDerm.org
Save time and money – consider registering online!

Guest Speaker

RACHAEL A. CLARK, MD, PHD

Associate Professor, Department of Dermatology; Harvard Medical School
Associate Dermatologist, Brigham And Women's Hospital; Boston, MA

Delivering the David Fretzin Lecture

Dr. Clark's laboratory emphasis is on the study of tissue resident memory T cells in health and disease. Her research is carried out largely on human cells and tissues, and it focuses on problems identified in clinical practice and has the dual goals of improving treatments for skin diseases while at the same time providing novel insights into human immune responses.

Dr. Clark received her medical degree and a PhD in immunology from Harvard Medical School in 1998. Her Internship was at the Mount Auburn Hospital. Dr. Clark completed her dermatology residency at the Massachusetts General Hospital in 2002 and a Research fellowship, Dermatology/Cutaneous Immunology, at Brigham and Women's Hospital in 2003.

She has numerous research projects and publications to her credit.

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Meeting Series"

October 8, 2014 *Chicago, IL*

OBTAINING YOUR CERTIFICATE OF CREDIT

Participants must attend the entire session to receive credit. Please be sure to sign the CME attendance sheet located the registration table before you leave the conference. Also, we ask that you complete the evaluation form and return it to the registration table upon. A certificate will be mailed to you upon conclusion of the meeting. The information collected as part of this process represents an important part of the CME planning process. The Colorado Foundation for Medical Care will retain a record of attendance on file for six years.

JOINT SPONSORSHIP STATEMENT

This educational activity is jointly provided by Colorado Foundation for Medical Care and the Chicago Dermatological Society.

GOAL / PURPOSE

To broaden the clinical knowledge of dermatologists.

FACULTY

Rachael Clark, MD, PhD
Associate Professor; Harvard Medical School
Boston, MA

EDUCATIONAL OBJECTIVES

Upon completion of the 2014-2015 series of meetings, participants should be able to:

1. Discuss key factors in the diagnosis and treatment for a variety of dermatologic diseases and conditions, including psoriasis, hair disorders, and dermatological symptoms of dermatologist.

2. Describe the manifestation of skin cancers and the efficacy of treatments available to the dermatologist.

3. List the therapeutic options available to the dermatologist for a variety of skin diseases, both medical and surgical, and discuss how new emerging treatments can be successfully incorporated into a dermatology practice

PHYSICIAN ACCREDITATION STATEMENT

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 the joint providership of the Colorado Foundation for Medical Care and the Chicago Dermatological Society. The Colorado Foundation for Medical Care is accredited by the ACCME to provide continuing medical education for physicians.

The Colorado Foundation for Medical Care designates this live activity for a maximum of 4.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

DISCLAIMER STATEMENTS

The content, views and opinions presented in this educational activity are those of the authors and do not necessarily reflect those of Colorado Foundation for Medical Care and Chicago Dermatological Society. The authors have disclosed if there is any discussion of published and/or investigational uses of agents that are not indicated by the FDA in their presentations. Before prescribing any medicine, primary references and full prescribing information should be consulted. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. The information presented in this activity is not meant to serve as a guideline for patient management.

OTHER HEALTHCARE PROFESSIONALS STATEMENT

This educational activity has been planned and implemented following the administrative and educational design criteria required for certification of health care professions continuing education credits. Registrants attending this activity may submit their certificate along with a copy of the course content to their professional organizations or state licensing agencies for recognition for 4.5 hours.

DISCLOSURE STATEMENT

Colorado Foundation for Medical Care insures balance, independence, objectivity, and scientific rigor in all our educational activities. In accordance with this policy, the Colorado Foundation for Medical Care identifies conflicts of interest with its instructors, planners, content managers, and other individuals who are in a position to control the content of an activity.

The following ***faculty, planner and/or content manager*** reported the following financial relationship with commercial interests whose products or services may be mentioned in this CME activity:

Dr. Clark has the following disclosures: Consulting fees - Stiefel, Novartis (served on scientific advisory board).

All other members of the faculty and planning team have nothing to disclose nor do they have any vested interests or affiliations.

Fee Information - There is no fee for this educational activity.

University of Illinois at Chicago
Department of Dermatology

FACULTY

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DERMATOPATHOLOGY

Marylee Braniecki, MD

PATHOLOGY

John V. Groth, MD
Elizabeth L. Wiley, MD

DERMATOLOGY RESIDENTS

Third Year

Sonoa Au, MD
Whitney Fancher, MD
Amanda Marsch, MD

Second Year

Monique Vanaman, MD
Rosemara Hughart, MD
Pauline Scott, MD
Drew Taylor, MD

First Year

Monica Boen, MD
Iona Chapman, MD
Kimberly Jerdan, MD
Eden Pappo, MD
Leigh Stone, MD

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Case Presented by Drew Taylor, MD
and Maria Tsoukas, MD, PhD

History of Present Illness:
A 61 year old African American male with a history of hepatitis C was referred to dermatology for a presumed fungal infection of the right thumbnail, clinically recalcitrant to a course of oral terbinafine. He noted a several month history of nail dystrophy and tenderness. He could not recall any prior trauma to the right thumb and denied any involvement of the remaining nails. The patient subsequently underwent a right thumbnail avulsion with no gross abnormalities of the nail bed or matrix appreciated. Shortly thereafter, the patient developed acute pain, swelling, and crusting of the right distal thumb. The nail bed was pan-cultured and the patient was started on empiric antibiotics and antifungals with no clinical improvement. A diagnosis of atypical pyoderma gangrenosum was entertained, prompting a trial of prednisone. Within a few days, the pain, swelling, and erythema had lessened. A quick tapering of the prednisone dose resulted in an acute, painful, pustular eruption involving the right distal thumb. A biopsy of the nail bed was performed.

Past Medical History:
Hepatitis C virus, genotype 1

Medications:
None

Allergies:
No known drug allergies

Family History:
No history of psoriasis, obesity, diabetes mellitus, or heart disease.

Social History:
The patient was a veteran with a remote history of illicit drug, ethanol, and tobacco use.

Review of systems:
The patient denied joint pain, fevers, chills, night sweats, or unintentional weight loss.

Physical Examination:
Erythema, crusting, and numerous pustules were present on the distal portion of the dorsal right thumb.

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

Diagnostic Procedures and Tests:
Bacterial culture: Streptococcus Group F, pan-sensitive
Periodic acid-Schiff stain and fungal culture: negative
Viral culture: negative

Histopathology:
Right thumb nail bed: There is prominent parakeratosis and conspicuous intra-corneal pustules. The epidermis displays prominent spongiosis with an underlying predominately perivascular chronic inflammatory infiltrate.

Diagnosis:
Acrodermatitis continua of Hallopeau

Treatment and Course:
Following the biopsy, the dose of prednisone was increased to 1mg/kg/day and the patient was also started on topical clobetasol ointment twice daily. Preliminary labs were obtained for potential therapeutic options with acitretin and/or biologics, and a radiograph of the right hand was ordered. Furthermore, a thorough discussion regarding psoriasis and its role as a marker for systemic inflammation was undertaken and appropriate referrals were placed.

Discussion:
Acrodermatitis continua of Hallopeau (ACH) is an extraordinary clinical entity. It is considered a subtype of pustular psoriasis with the potential to evolve into a generalized pustular psoriasis, the von Zumbusch type. Additionally, ACH has recently been reported to be a clinical phenotype of DITRA (deficiency of the IL-36R antagonist) lending further insight into the humbling complexity of the proposed immunologic aberrations.

The disease is characterized by a chronic, relapsing course with development of sterile pustules that initially affect the distal fingers or toes. Eighty percent of cases start in only one digit, with most cases instigated by trauma or infection. Interestingly, terbinafine is known to exacerbate psoriasis or induce psoriasis de novo. A recent case report linked oral terbinafine to the development of ACH. Complications from chronic inflammation include atrophy, osteolysis, and syndactyly of the digits. Also, a perplexing case of reflex sympathetic dystrophy following unilateral ACH has been described in the literature.

Diagnosis is established through histopathological examination, as a number of dermatologic conditions can masquerade clinically as ACH. Histologically, ACH displays features of pustular psoriasis.

Treatment of ACH is historically lackluster given its refractory nature to typical anti-psoriatic agents. Recent case reports have reported improvement with biologic agents alone or in conjunction with methotrexate, cyclosporine or retinoids. Psoriasis is now recognized to be more than skin deep and treatment guidelines must reflect this ideology in order to optimize patient care. Patient education, appropriate referrals, and encouraging a healthy lifestyle will yield dividends in modifying the associated cardiovascular risk factors. Dermatologists must take psoriasis not as a cosmetic concern but as a systemic one.

Essential Lessons:
- ACH is a rare entity and diagnosis is difficult to recognize given the natural evolution of the disease.
- Reports have suggested TNF inhibitors are an excellent addition to our ACH therapeutic armamentarium.
- The associated cardiovascular disease risk factors seem to be plastic.

References:

1. Bolognia JL, et al. Chapter 9: Psoriasis *in* Dermatology, Second Edition, Elsevier Limited, 2008:121-22.
2. Journal of the American Academy of Dermatology (Producer) 2014. Vascular Inflammation in Psoriasis Localizes to the Arterial Wall [Audio podcast]. Retrieved from http://itunes.apple.com
3. Puig L, et al. Treatment of acrodermatitis continua of Hallopeau with TNF-blocking agents: case report and review. *Dermatology*. 2010;220(2):154–58.
4. Razera F, et al. Neutrophilic dermatoses: part II. *An Bras Dermatol*. 2012;86(2):195-209.
5. Ryan C, et al. Treatment of acrodermatitis continua of Hallopeau with adalimumab. *Br J Dermatol*. 2009; 160(1):203–5.
6. Sehgal VN, et al. Acrodermatitis continua of Hallopeau: evolution of treatment options. *Int Dermatol*. 2011; 50(10): 1195-211.
7. Szepietowski JC. Terbinafine exacerbates psoriasis: case report with a literature review. *Acta Dermatovenerol Croat*;2003;11:17–21.

Case Presented by Sonoa Au, MD
and Jane Scribner, MD

History of Present Illness:
This 64 year old male with a history of liver cirrhosis, ascites and associated umbilical herniation presented with a several week history of painless draining papules at the site of his umbilical hernia. His umbilical hernia had been present for three years, and had been reducible until several months ago, at which time the overlying skin became thickened and dark, and the papules started to develop. He had not initiated any therapy for the lesions.

Past Medical and Surgical History:
Liver cirrhosis secondary to chronic alcoholism and Hepatitis B, ascites, esophageal varices, anemia, diabetes mellitus, duodenal ulcer, diverticulosis

Medications:
Furosemide, omeprazole, spironolactone, thiamine

Allergies:
Celecoxib

Social and Family History:
This patient had a history of alcohol abuse but quit several months prior to presentation. He had been smoking for almost 50 years, and continued to smoke 1 pack per day. He was deployed to Vietnam for 2 years, and subsequently worked as a field engineer, but was unaware of any asbestos exposure. He denied illicit drug use. He had no contributory family history of malignancies.

Review of Systems:
The patient had discomfort due to abdominal distention. He denied fevers, vomiting, recent weight changes, shortness of breath, chest pain, bowel or urinary changes.

Physical Examination:
The patient had a distended abdomen and a large non-reducible umbilical subcutaneous mass with coarse, cobblestoned hyperpigmented skin and many smaller than 5mm skin colored to translucent papules and vesicles at the base of the mass circumferentially. There was yellow serous discharge from the papules and vesicles which was more prominent while the patient was upright compared to supine.

Laboratory Data, Diagnostic Procedures and Tests:
12/13 **Positron emission tomography–computed tomography:** Low to moderate FDG avidity localizing to the protruding mass-like thickening of the umbilicus, presumed to represent to patient's mesothelioma site; large volume ascites and cirrhotic morphology of the liver.
06/14 **Cytology, peritoneal fluid:** Atypical mesothelial proliferation including three dimensional clusters and rosettes.

Histopathology:
Umbilicus, skin: The lesion is centrally ulcerated, and elsewhere covered in hyperplastic but otherwise uninvolved epidermis. Diffuse sheets of discohesive epithelioid cells with clear to amphophilic cytoplasm are seen filling most of the dermis. Focal papillary structure formation is observed. There is prominent nuclear pleomorphism but mitotic figures are not seen. The nuclei contain coarse chromatin and inconspicuous nucleoli. The following stains are positive: calretinin, D2-40, WT1, HBME-1, pancytokeratin and CK7. Negative stains include: CD10, CK20, CEA, CD31, CD34, CD163, Ber-EP4, and HepPar1.

Diagnosis:
Clear cell mesothelioma

Treatment and Course:
The patient underwent excision of the umbilical mass, thought initially to be a hernia repair. The skin and soft tissue specimen sent to pathology confirmed the diagnosis of clear cell mesothelioma, with extensive infiltration of the dermis by atypical mesothelial cells. Due to severe recurrent ascites and elevated portal venous pressures, the patient will undergo a transjugular intrahepatic portosystemic shunt (TIPS) procedure prior to receiving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

Discussion:
Malignant mesothelioma is a neoplasm that arises from the cells of the mesothelium lining the pleura, pericardium, peritoneum or rete testis, and is most commonly associated with asbestos exposure. Clear cell mesothelioma, a variant of epithelial mesothelioma, is an exceedingly rare entity that has only been described in a few case reports. To the authors' knowledge, this is the first case with a cutaneous presentation.

Clear cell mesothelioma is characterized by large polygonal cells with abundant clear cytoplasm that form papillary structures. Since malignancies from other organs can have a clear cell morphology, immunohistochemical analysis is vital in confirming the diagnosis. Calretinin is regarded as one of the most sensitive and specific mesothelioma markers, and stains both the nucleus and cytoplasm. D2-40 is another marker that is very sensitive and specific, and can distinguish clear cell mesothelioma with other clear cell adenocarcinomas of various origins. Wilm's tumor 1, HBME-1, Cytokeratin 7 and cytokeratin 5/6 are additional positive markers for these tumors.

Peritoneal mesothelioma accounts for less than 20% of mesotheliomas, with pleural mesotheliomas accounting for the majority of cases. Patients usually present with abdominal discomfort and distension due to ascites. Clinically, peritoneal mesotheliomas present either as wet or dry-painful types. Our patient's presentation is classified as the wet type as he has massive ascites without significant evidence of a solid tumor on computed tomography (CT). The dry-painful type typically lacks ascites but presents with a solid mass confined to a part of the abdomen producing pain.

There are no formal staging criteria for peritoneal mesothelioma. Prognosis for patients with mesothelioma is poor, but patients with very early stage disease may be responsive to surgical resection. Otherwise, treatment usually involves palliative chemotherapy and radiation. Hyperthermic intraperitoneal chemotherapy (HIPEC) is a procedure that can be used for a number of malignancies that involve the peritoneal lining, and are confined to the peritoneal cavity. It involves surgical exploration and debulking of the visible tumor, followed by continuous circulation of a heated chemotherapeutic agent throughout the peritoneal cavity for a maximum of two hours. Prior to HIPEC, the median survival with chemotherapy was one year, and various studies have shown the median survival time to at least double with the use of the procedure.

Essential Lesson:
- Mesothelioma should be considered in the differential diagnosis of skin tumors, particularly in older individuals presenting with ascites and a history of asbestos exposure.

References:

1. Dessy E, et al. Unusual clear cell variant of epithelioid mesothelioma. *Arch Pathol Lab Med.* 2001; 125(12):1588-90.
2. Ordóñez NG. Clear cell mesothelioma presenting as an incarcerated abdominal hernia. *Virchows Arch.* 2005;447(5):823-7
3. Abban C, Viglione M. Peritoneal mesothelioma presenting as a skin nodule. *J Cutan Pathol.* 2009;36(6):675-9.
4. Yan TD, et al. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. *Ann Oncol*. 2007;18(5):827-34.

Case Presented by Monique Vanaman, MD
and Michelle Bain, MD

UNKNOWN CASE

This 64 year old male presented with a lesion on the left temple.

Case Presented by Iona Chapman, MD, Maria Tsoukas, MD, PhD and Iris K. Aronson, MD

History of Present Illness:
This 45 year old Hispanic female with history of systemic lupus erythematosus (SLE), mixed connective tissue disorder and Raynaud's disease presented with a rash on her face and arms. Although present for a total of four months, the rash could clear for approximately one week at a time. The rash was intermittently present on her forehead and cheeks, but worse on her arms and hands. Pruritus and burning was present, exacerbated by showering with warm water. When her eruption first began, she received an unknown shot and a methylprednisolone dose pack from her primary care physician. When the rash flared after completing the pack, her rheumatologist prescribed prednisone 20 mg daily with a slow taper. A month later, she was continued on prednisone 7.5 mg and started on azathioprine 100mg daily. She had had two rituximab infusions five months prior to presentation for arthralgias with significant improvement.

Past Medical History:
SLE, mixed connective tissue disorder, Raynaud's disease, fibromyalgia, gastroesophageal reflux disease, depression and thrombotic thrombocytopenic purpura (seven years prior to presentation)

Medications:
Acetaminophen-codeine #3, albuterol inhaler, aspirin, azathioprine, calcipotriene 0.005% cream, diclofenac 1% gel, ergocalciferol, escitalopram, folic acid, gabapentin, multivitamin, nifedipine, pantoprazole, pentoxifylline, prednisone, silver sulfadiazine, tramadol

Allergies:
Meloxicam, zolpidem

Family History:
Mother with non-melanoma skin cancer.

Social History:
The patient was married and denied any tobacco, alcohol or illicit drug use.

Review of Systems:
The patient reported fatigue, arthralgias and oral ulcers, but denied fever, chills, and weight loss.

Physical Exam:
The patient had faint erythema on the malar cheeks. Her arms had several discoid erythematous edematous blanchable non-scaly plaques with surrounding hypopigmentation, most numerous over the extensor surfaces. Her hands had periungual erythema and swelling over the second and third metacarpophalangeal joints.

Laboratory Data:
The following were positive or abnormal:
Alkaline phosphatase 34 u/l (40-125), albumin 3.3 g/dl (3.4-5.0), absolute lymphocytes 1.0 thousands per ul (1.3- 4.2), dsDNA titer 1:160 (<1:10), C3 30 mg/dl (79-152), C4 <5 mg/dl (12-47)

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

Diagnostic Procedures and Tests:
None

Histopathology:
Left arm, skin: The papillary and upper reticular dermis contain a moderate perivascular neutrophilic infiltrate with conspicuous karyorrhexis. There is focal vacuolar interface change. Extravasated red blood cells and fibrinoid vascular changes are absent. Colloidal iron highlights mildly increased dermal mucin and PAS is negative for fungal organisms.

Diagnosis:
Systemic lupus erythematosus-associated neutrophilic dermatosis

Treatment and Course:
Rheumatology elected to maintain the azathioprine dose and complete another two rituximab infusions. At her follow up visit with rheumatology, her dsDNA had increased to 1:2560. She was temporarily placed on prednisone 10 mg daily, azathioprine 150 mg daily and received one infusion of solumedrol 1 g. She later completed another two infusions of rituximab. At her five-month follow-up, the patient reported significant improvement in her cutaneous lesions.

Discussion:
Systemic lupus erythematosus-associated neutrophilic dermatosis is an infrequently observed variant of SLE. It has been described under broader terms such as neutrophilic urticarial dermatosis and non-bullous neutrophilic dermatosis, and specifically as nonbullous neutrophilic lupus erythematosus. Ackerman first described the histology of these lesions in 1997, noting a papillary and superficial reticular dermal infiltrate of neutrophils with a “neutrophilic dust.” Gleason et al. then reported 4 patients with “non-bullous neutrophilic dermatosis” in 2006 and several other reports of small numbers of patients have since been published. Diagnosis lies within histological examination rather than the clinical presentation. As described in detail below, careful histological review can elucidate characteristics that help distinguish this disease from Sweet’s syndrome, leukocytoclastic vasculitis and other diseases that have similar characteristics. Larson and Granter point out that SLE-associated neutrophilic dermatosis may be the initial presentation of SLE, making this disease all the more important to understand and be able to recognize.

One of the larger case reports was presented by Larson and Granter, describing 14 patients with biopsy proven neutrophilic dermatosis. 13 patients were female with a mean age of 42.8. A smaller case study by Brinster et al. reported 4 patients, all female, with a mean age of 35.5. Lesions were noted as urticarial or erythematous papules and plaques and occurring most commonly on the extremities. In the series of 4 patients presented by Gleason et al., three patients presented with systemic symptoms, such as fever, malaise, arthritis and lymphadenopathy, similar to some of the systemic symptoms seen in the 3 SLE patients described in the case report by Kieffer et al.

Histology reveals sparse to dense neutrophilic infiltrate. In the series described by Larson and Granter, 5 out of the 14 patients had a sparse infiltrate while 7 of the 14 had a moderate infiltrate, but all 12 had karyorrhexis. Compared to Sweet’s syndrome, Brinster et al. noted that SLE-associated neutrophilic dermatosis has a less dense neutrophilic infiltrate and lacks the papillary edema seen in Sweet’s syndrome. In addition, presence of an interface dermatitis and dermal mucin support a diagnosis of SLE-associated neutrophilic dermatosis, although Larson and Granter found that only just over half the 14 patients demonstrated the former and only 4 demonstrated the latter, making the distinction somewhat less clear-cut. Although there can be red blood cell extravasation (for example, in 5 of Larson and Granter’s 14 patients), there is no fibrinoid vascular change, helping to distinguish SLE-associated neutrophilic dermatosis from leukocytoclastic vasculitis. In his original histological description of SLE-associated neutrophilic dermatosis, Ackerman suggested this was a form fruste of bullous LE. However, Larson and Granter caution that this histological correlation is not manifested as development of bullae in the initial lesions of SLE-associated neutrophilic dermatosis.

It has been suggested that the pathogenesis of SLE-associated neutrophilic dermatosis is through an antibody-mediated mechanism. 3 of the 4 patients presented by Brinster et al. had a DIF performed in which 2 of the 3 showed staining at the dermoepidermal junction. All 4 of the patients with DIF in Larson and Granter’s patient pool had findings at the dermoepidermal junction, lending support to this theory.

The treatment of SLE-associated neutrophilic dermatosis is based upon immunosuppression. 3 of the 4 patients in the group presented by Brinster et al. were already on one or multiple immunosuppressants. The increase of current therapy or the addition of another immunosuppressant led to clinical resolution. The fourth patient cleared with addition of a topical steroid alone.

In summary, systemic lupus erythematosus-associated neutrophilic dermatosis is a unique variant of neutrophilic dermatosis. Careful histological review of biopsy specimens reveals features that help secure the diagnosis.

Essential Lessons:

- Systemic lupus erythematosus-associated neutrophilic dermatosis is a rare, but important variant of neutrophilic dermatosis.
- Histology reveals a neutrophilic infiltrate, interface dermatitis, dermal mucin, and possible RBC extravasation without fibrinoid vascular change, helping to distinguish this disease from related and similar diseases.

References:

1. Ackerman AB. Histologic diagnosis of inflammatory skin diseases: an algorithmic method based on pattern analysis. 2nd ed. Baltimore: Williams and Wilkins; 1997. P. 525-532, 542-543.
2. Brinster NK et al. Nonbullous neutrophilic lupus erythematosus: A newly recognized variant of cutaneous lupus erythematosus. *J Am Acad Dermatol.* 2012 66(1): 92-97.
3. Gleason BC et al. Non-bullous neutrophilic dermatosis: an uncommon dermatologic manifestation in patients with lupus erythematosus. *J Cutan Pathol*. 2006;33(11): 721-5.
4. Kieffer C et al. Neutrophilic urticarial dermatosis: a variant of neutrophilic urticarial strongly associated with systemic disease. Report of 9 new cases and review of the literature. *Medicine.* 2009;88(1): 23-31.
5. Larson AR, Granter SR. Systemic lupus-erythematosus-associated neutrophilic dermmatosis- an underrecognized neutrophilic dermatosis in patients with systemic lupus erythematosus. *Hum Pathol*. 2014;45(3): 598-605.

Cases Presented by Whitney Fancher, MD, Jane Scribner, MD, and Sophie Worobec, MD

Patient A

History of Present Illness:

This 30 year old male presented for continued laser treatment of rosacea, previously diagnosed and treated by an outside dermatologist. The patient first noted a persistent red patch on his right neck seven years prior, which was followed one year later by episodic facial flushing exacerbated by stress, anxiety, sexual activity, and alcohol consumption. A few episodes of flushing had been accompanied by palpitations and one episode accompanied by shortness of breath. He also noted that he was taken to the emergency department for lightheadedness after a bee sting two years prior to presentation. He admitted to taking multiple supplements on a daily basis but had started these supplements years after the onset of flushing. He denied itching, pain, fever, chills, nausea, vomiting, diarrhea, abdominal pain, headaches, or loss of consciousness. The patient noted minimal improvement with topical metronidazole gel and four pulsed dye laser treatments as received by an outside dermatologist.

Past Medical and Surgical History:

Rosacea, attention deficit disorder, appendectomy

Medications:

Hydroxycut, Cellucorx4 supplement (caffeine, protein, creatine, nyacine), testosterone supplement

Allergies:

No known drug allergies

Family History:

No family history of malignancy or skin or autoimmune disease.

Social History:

The patient is an active duty Navy diver with no alcohol, tobacco, or drug use.

Review of Systems:

The patient noted a few episodes of palpitations and shorteness of breath associated with flushing. He denied malaise, fever, chills, night sweats, chest pain, nausea, vomiting, diarrhea, abdominal pain, cramping, weight loss, bone pain, arthralgia or myalgia.

Physical Examination:

The patient had bilateral faint malar erythema as well as brighter patchy erythema of the right lateral cheek, right lateral neck, and right ear lobule extending up to the mid-helix.

Laboratory Data:

The following were positive or abnormal:
Tryptase, serum 81 ng/mL, repeat 74 ng/mL (<11.5)
5-HIAA, 24hr urine 9.3mg (0-6)

The following were negative or within normal limits:
Complete blood count with differential and peripheral smears, complete metabolic panel, Immunoglobulin E, Antinuclear antibody, Chromogranin A, Human Immunodeficiency Virus, fasting lipid profile

Diagnostic Procedures and Tests:

11/13 **Positron emission tomography–computed tomography:** Negative for masses
11/13 **Bone marrow biopsy:** Tryptase staining with two aggregates consisting of slightly more than 15 mast cells in a perivascular position. Cells are CD117 and CD25 positive and CD2 negative. No mutation detected in c-Kit gene.

06/14 **Bone marrow biopsy:** Normocellular bone marrow with scattered aggregates of mast cells, some with greater than 15 mast cells, which co-express CD25. c-Kit mutation negative. No evidence of myelodysplasia or other co-existing neoplasm. No significant eosinophilia or fibrosis. Flow cytometric analysis does not detect an increased mast cell population or evidence of a myeloid or lymphoid neoplasm. Cytogenic studies normal. Mast cell infiltrates in the marrow do not appear dense or of atypical morphology.

05/14 **Transthoracic echocardiogram:** Normal valvular morphology and function.

Histopathology:
Right neck, skin: There is slight orthohyperkeratosis but an otherwise unremarkable epidermis. There are increased ectatic blood vessels present in the papillary dermis, accompanied by a superficial perivascular and interstitial infiltrate composed of numerous spindle and polygonal cells. The spindle cells have hyperchromatic nuclei. The polygonal cells contain abundant amphophilic cytoplasm and numerous small, faintly visible granules; their nuclei are centrally placed, giving a "fried egg" appearance. The cells stain positive with CD117/c-kit and tryptase as well as CD2 and CD25.

Diagnosis:
Indolent systemic mastocytosis with telangiectasia macularis eruptiva perstans (TMEP)

Treatment and Course:
The patient was prescribed oral ceterizine 10mg daily and rantitidine 150mg daily for histamine blockade. He has noted improvement in redness and flushing. He follows with hematology-oncology every six months and carries an epipen with him at all times.

Patient B
History of Present Illness:
This 45-year-old male presented for evaluation of moles present for many years. The patient also noted many asymptomatic brown spots on his trunk for many years. He had no personal or family history of skin cancer.

Past Medical and Surgical History:
Hypertension

Medications:
None

Allergies:
No known drug allergies

Family History:
There was no family history of malignancy or skin disease.

Social History:
The patient smoked 4 cigarettes per day and consumed 1-2 alcoholic drinks per day.

Review of Systems:
The patient noted 1-2 episodes of loose stools per week. He denied palpitations, shorteness of breath, flushing, chest pain, nausea, vomiting, diarrhea, abdominal pain or cramping, weight loss, muscle/joint/bone pain.

Physical Examination:
The patient had multiple tan to light brown macules on his shoulders, upper arms, and trunk along with multiple pink to red-brown macules scattered on his chest, abdomen, and flanks. Darier's sign was elicited upon rubbing a pink-brown oval macule on the right flank.

Laboratory Data:
The following were positive or abnormal:
Tryptase, serum 13 ng/mL (<10.9)

The following were negative or within normal limits:
Complete blood count with differential, complete metabolic panel, Tissue transglutaminase
Immunoglobulin A

Diagnostic Procedures and Tests:
09/14 **Computed tomography, chest**: Several tiny micronodules.
09/14 **Computed tomography, abdomen and pelvis:** Diffuse bladder wall thickening.

Histopathology:
Right flank, skin: There is a prominent and diffuse superficial dermal infiltrate composed of predominately epithelioid cells and fewer spindle cells, which are distributed in a linear array. The epithelioid cells have oval to round nuclei with vesicular chromatin, inconspicuous nucleoli and abundant amphophilic cytoplasm. The spindle cells have sparse cytoplasm and hyperchromatic nuclei. The cells stain diffusely positive for CD117.

Diagnosis:
Cutaneous mastocytosis, telangiectasia macularis eruptiva perstans (TMEP) variant .
Ephelides, solar lentigines, nevocelular nevi

Treatment and Course:
The patient continues follow-up with hematology-oncology and dermatology. After discussion with the patient and given lack of evidence of systemic involvement, the plan per hematology-oncology is to hold off on bone marrow biopsy at this time with repeat labs and chest CT in 6 months.

Discussion:
Mastocytosis is a term that describes local or systemc accumulations of mast cells. It can be viewed as a myelodysplastic disorder or a rare myeloid malignancy characterized by abnormal accumulation of CD34+ bone marrow-derived mast cells (MCs) in one or more tissues, most commonly the skin, bone marrow (BM), and gastrointestinal tract followed by the liver, spleen, and lymph nodes. It occurs in all ethnicities and may present at any age. Most adult cases are sporadic and associated with somatic activating mutations involving codon 816 of the c-KIT proto-oncogene. c-KIT encodes the tyrosine kinase KIT, the receptor for stem cell growth factor on mast cells and hematopoetic stem cells; mutations in codon 816 of c-KIT lead to mast cell proliferation.

Mastocytosis is divided into two main categories: cutaneous mastocytosis (CM) and systemic mastocytosis (SM). In CM, the MC infiltrate is confined to one or more skin lesions. The World Health Organization (WHO) classification of CM includes three subvariants: (i) nodular cutaneous mastocytosis (mastocytoma); (ii) diffuse cutaneous mastocytosis; and (iii) urticaria pigmentosa (UP) which includes the rare plaque, nodular, and telangiectatic (telangiectasia macularis eruptiva perstans, TMEP) variants. SM is characterized by MC infiltration of at least one extracutaneous organ with or without skin involvement.

Children with mastocytosis commonly present with skin lesions of UP or mastocytomas within the first year of life, have no systemic involvement, and experience resolution or fading of lesions by adolescence. In contrast, adult mastocytosis is almost always associated with BM involvement and has a persistent course.

Systemic symptoms are common in all forms of mastocytosis, secondary to the effects of secreted mast cell mediators, including histamine, cytokines, prostaglandins, and leukotrienes, acting usually on the blood vessels, respiratory tree, or gastrointestinal tract. These symptoms include pruritus, flushing, urticaria, angioedema, headache, nausea, vomiting, abdominal cramps, diarrhea, gastric and/or duodenal ulcer, malabsorption, asthma-like symptoms, presyncope, syncope, and anaphylaxis. Symptoms may occur spontaneously or may be the result of massive histamine release after ingestion of known mast cell

degranulators, such as alcohol, morphine, codeine, or extended rubbing of the skin. Symptoms may be exacerbated by exercise, heat, emotional upset, and local trauma to skin lesions. *Hymenoptera* stings and general anesthesia may induce anaphylaxis. Mast cells also produce heparin, which may result in hematemesis, epistaxis, melena, and ecchymoses. Osteoporosis may also occur from chronic heparin release, resulting in fractures. Complaints of bone pain, fever, night sweats, malaise, weight loss, epigastric distress, and congnitive disorganization often signal the presence of extracutaneous disease.

CM is diagnosed via skin biopsy showing perivascular mast cell infiltrate in the upper dermis; infiltrates may be seen on hemotoxylin and eosin stain but are highlighted by giemsa, toluidine blue, and immunohistochemical c-kit (CD117) and tryptase stains which are very sensitive. TMEP is the least common form of CM, primarily seen in adults, and characterized by progressive tan, red–tan, or brown telangiectatic macules and patches; non-telangiectatic lesions may be present. Lesions are numerous and symmetrically scattered, mostly in a truncal distribution; unilateral and facial TMEP have been described. Lesions are commonly asymptomatic given that MCs are usually few in number, but they can be pruritic and exhibit a Darier's sign (urtication of lesional skin when stroked, due to mast cell degranulation). Though less common than with other forms of adult-onset CM, systemic involvement may occur.

Most patients with SM have indolent disease (ISM), meaning bone marrow examination shows abnormal mast cell aggregates but no other hematologic disease and no evidence of end-organ damage secondary to mast cells. Serum tryptase level has been shown to correlate with mast cell burden and is considered an adequate noninvasive screening test for SM. However, given that the majority of patients with adult-onset mastocytosis have BM involvement when skin lesions are detected, recent guidelines recommend BM biopsy in all adult patients with CM, even in the absence of clinical symptoms, c-KIT mutation, or elevated tryptase levels. Given that most cases of SM, especially those with cutaneous involvement, are ISM, and that ISM is often managed the same way as CM, patients should be counseled on BM biopsy. For patients who decline BM biopsy and have no clinical signs or symptoms of organ damage or evidence of hematologic neoplasm, a provisional diagnosis of CM may be maintained without further workup aside from annual monitoring as described below.

Diagnosis of SM is made according to the WHO criteria, of which there are one major and four minor ones (Table 1). For diagnosis of SM, a patient needs to meet either the major and one minor or three minor criteria. Patients with cutaneous and systemic disease should be monitored at least once yearly with physical examination and complete blood count and serum tryptase level measurements. Initial or repeat BM biopsy should be performed if there is elevation of the tryptase level, a drop in the platelet count or hemoglobin, a rise in the monocytes, or the onset of organomegaly.

Table 1. Diagnostic criteria of Systemic Mastocytosis (SM)*

Major

- Multifocal dense aggregates of mast cells with more than 15 cells per aggregate in extracutaneous tissue

Minor

1. Greater than 25% of mast cells have morphologic abnormalities such as spindle shapes, cytoplasmic projections, hypogranulation tissue
2. Expression of CD25 with or without CD2 by mast cells
3. Detection of a codon 816 c-kit mutation by a sensitive technique in lesional tissue or peripheral blood
4. Serum tryptase greater than 20ng/mL

*The major and one minor or three minor criteria required for diagnosis

Prognosis of patients with CM and ISM is very good, with life expectancy unchanged from age- and sex-matched controls. Treatment of mastocytosis includes avoidance of mast cell degranulation and inhibiting the actions of released mediators. Avoidance of triggers such as extremes of temperature, pressure/friction, and chemical degranulators of mast cells, is important. Chemical degranulators include opiates, aspirin, alcohol, quinine, scopolamine, gallamine, decamethonium, reserpine, amphotericin B, polymyxin B, and d-tubocurarine. Given that *Hymenoptera* stings may induce anaphylaxis, the patient should carry with them a premeasured dose of epinephrine (Epipen) for emergency use. Antihistamines

(H1 and H2 blockers) control pruritus, flushing, and gastric hyperexcretion in most patients. Topical or intralesional corticosteroids, psoralen + ultraviolet A (PUVA) phototherapy, and pulsed-dye laser have been effective in improving cutaneous lesions. Diarrhea may be treated with cromolyn sodium, and gastrointestinal ulcers may be treated with H2 blockers or proton pump inhibitors. ISM is commonly managed as CM, with trigger avoidance and antihistamines. Advanced stages of mastocytosis may require cytoreductive therapy, including interferon alpha combined with glucocordicoids, cladribine, or combination chemotherapy followed by stem cell transplant in highly aggressive or relapsed cases.

Essential Lessons:

- Mastocytosis is a myelodysplastic disorder/myeloid malignancy characterized by abnormal accumulation of mast cells in one or more tissues, most commonly the skin, bone marrow, and gastrointestinal tract.
- Symptoms of flushing, pruritus, abdominal pain, diarrhea, palipitations, and light-headedness or syncope should prompt screening for mastocytosis with serum tryptase levels.
- The majority of adult patients with cutaneous mastocytosis will have systemic disease as well, with indolent disease being most common.
- Trigger avoidance and antihistamines are the mainstay of treatment for cutaneous mastocytosis and indolent systemic mastocytosis.

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Case Presented by Rosemara Hughart, MD
Claudia Hernandez, MD and Aleksandar Krunic, MD, PhD

Fast Break: A Case of Melanonychia Striata

Case Presented by Leigh Stone, MD
and Milena Lyon, MD

History of Present Illness:
This 46 year old Hispanic male with acquired immunodeficiency syndrome presented with lesions on his right dorsal hand and arm for four weeks. He noted an initial pimple-like lesion on his right dorsal hand. Subsequently, he developed multiple red, tender bumps extending in a stepwise fashion up his right arm. He denied gardening, pets or fish tank at home, and recent travel.

Past Medical History:
Acquired immunodeficiency syndrome with poor medication adherence, cryptococcal meningitis, seborrheic dermatitis, herpes zoster, recurrent oral candidiasis, recurrent otitis media, hypertension, type 2 diabetes mellitus

Medications:
Trimetheprim-sulfamethoxazole, hydrochlorothiazide, metformin, lisinopril

Allergies:
No known drug allergies

Social History:
The patient was born in Mexico and immigrated to the United States in 1987. He lived with his wife and their three children. He was infected with HIV through heterosexual intercourse presumably while in the Mexican military. He did not smoke or use intravenous drugs. He drank alcohol occasionally. He worked part time as a tax preparer.

Review of systems:
He reported fevers, chills, night sweats, and myalgias.

Physical Examination:
The patient had erythematous nodules on the right dorsal hand, lateral wrist, forearm, and upper arm. No axillary lymphadenopathy was appreciated.

Laboratory Data:
The following were positive or abnormal:
White blood cells 3.5 k/µl (3.9-12.0)
Red blood cells 2.87 million/ul (4.0-6.1)
Hemoglobin 8.9 g/dl (13.2-18.0)
Hematocrit 27.2% (38-55)
Absolute lymphocytes 0.4 k/µl (1.3-4.2)
Helper T cell % (CD3/CD4) 1 (32-55)
Absolute CD4 count 5 (267-1120)

The following were negative or within normal limits:
Blood cultures times two

Diagnostic Procedures and Tests:
04/14 **Culture, bacterial:** Methicillin-sensitive *Staphylococcus aureus*
04/14 **Culture, fungal:** No growth after four weeks
04/14 **Culture, acid fast bacilli:** No acid fast bacilli isolated after eight weeks

Histopathology:
Right arm, skin: The epidermis shows slight acanthosis and spongiosis with overlying parakaratosis. The dermis contains a superficial and deep perivascular and diffuse interstitial lymphohistiocytic infiltrate with

prominent admixed neutrophils. There is prominent endothelial swelling with focal areas of vascular ectasia and RBC extravasation. AFB, Fite, GMS, and PAS stains are negative for mycobacterial and fungal organisms.

Diagnosis:
Sporotrichoid lymphangitis due to *Staphylococcus aureus*

Treatment and Course:
The patient was evaluated by infectious disease the day prior to his initial dermatology clinic visit, and his dose of trimetheprim-sulfamethoxazole was increased from daily to twice daily. He continued this regimen and was markedly better in one week; the nodules were resolving and he was no longer febrile.

Discussion:
Sporotrichoid lymphangitis is an infectious process characterized by discrete, erythematous nodules distributed in a linear fashion from distal to proximal on an extremity. In the United States, the most common cause of this cutaneous presentation is its namesake: *Sporothrix schenckii.* Other pathogens include atypical mycobacteria, *Nocardia* species, *Leishmania* species, and *Francisella tularensis*. Though common causes of skin infections, pyogenic bacteria such as *Staphylococcus aureus (S. aureus)* are considered an uncommon cause of sporotrichoid lymphangitis. Certain exposures, such as soil for S*porothrix* or fresh/saltwater for *Mycobaterium marinum*, are considered important diagnostic clues when evaluating a patient with sporotrichoid lymphangitis.

To our knowledge, there are only four case reports in the literature of *S. aureus* causing sporotrichoid lymphangitis. Though some were reports of previously healthy individuals, other cases mention immunosuppression in the hosts through various means. We did not find a case where the patient was similarly afflicted with acquired immunodeficiency syndrome. This case illustrates the importance of considering S*. aureus* as the causative organism of sporotrichoid spread.

Essential Lesson:
- Consider *Staphylococcus aureus* as a causative agent of sporotrichoid spread.

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Case Presented by Monica Boen MD and Lawrence Chan, MD

History of Present Illness:
Dermatology was consulted to evaluate a 6 day old female born to a 28 year old G7P3043 mother and a 40 year old father at 37 weeks via normal vaginal delivery with birth weight in the 3rd percentile (2,200mg). At birth, the patient presented with lack of eyelids, eyebrows and eyelashes, corneal ulcers, macrostomia, abnormal ears, alopecia of the scalp, and wrinkled and xerotic skin with scaly plaques. During pregnancy, the mother admitted to drinking alcohol a few times per month during the 2nd and 3rd trimester and received poor prenatal care. Of note, the mother's previous 2 children with another father, ages 5 and 8, are healthy with no observable cutaneous or cranio-facial abnormalities.

Prenatal history:
Maternal age/parity: 28 year old G7P3043
Vaginal birth
Pregnancy complications: mother with diabetes and hypertension, and poor prenatal care

Medications:
None

Allergies:
None

Family History:
No family history of genetic disorders on mother's side. Patient's father's family history was unknown.

Social History:
Mother was a homemaker
Mother and patient's maternal grandmother had co-guardianship of the child

Physical Examination:
The patient's initial ocular examination at 6 days of age was significant for the lack of eyelids, eyelashes, and eyebrows, hypertelorism, corneal clouding and conjunctival erythema. She had hypoplastic and malformed ears, and an enlarged mouth with a thin upper lip. She had alopecia of her scalp, as well as a lack of lanugo hair. The umbilicus was inserted at a higher position than normal and there was genital hypoplasia. She had diffuse severely xerotic skin and redundant skin folds.

Diagnosis:
Ablepharon Macrostomia Syndrome

Treatment and Course:
After birth, the patient was placed in a neonatal intensive care unit for close monitoring. Frequent ocular lubricants and antibiotics were administered. A karyotype and microarray analysis showed a normal female karyotype. Patient had emergent bilateral corneal transplants and eyelid reconstruction at 12 days old due to severe corneal thinning and a high potential for corneal perforation. At 2 weeks of age, the patient had temporary bilateral tarsorrhaphy, a surgical procedure to close the eyelids to preserve corneal function, with several later revisions. Audiology testing revealed normal hearing. At 7 weeks of age, the patient's skin was much improved with daily administration of petrolatum and was no longer xerotic.

Discussion:
Ablepharon macrostomia syndrome (AMS) was first described by McCarthy and West in 1977 in two unrelated male children. AMS is a very rare multiple congenital malformation syndrome that includes the following features: severely shortened or absent eyelids, absence of eyebrows and eyelashes, fusion defects of the mouth, abnormal ears, ambiguous genitalia, and xerotic and redundant skin. There have

been 17 reported cases of AMS in the literature. These cases were mainly reported in children, and there are only 4 documented cases of adults with AMS.

All of the reported patients with AMS had a normal karyotype, except for one patient that had a complex rearrangement in chromosome 18q with a de novo paracentric inversion with an interstitial deletion (Pelligrino et al 1996). However, this patient presented with additional abnormalities other than the classic features of AMS, such as seizures, spastic quadriplegia, and severe developmental delays to suggest that the chromosome 18q rearrangement maybe an incidental finding and not the locus of the gene abnormalities in AMS. The most likely inheritance pattern of AMS is autosomal dominant based on two confirmed familial occurrences of AMS. Ferraz et al (2000) reported a father with partial AMS who had two daughters with AMS, and Rohena et al (2011) described both a father and daughter with full expression of the AMS phenotype.

Other clinical features of AMS include short stature, camptodactyly, and hypertelorism. While patients have abnormal ears, the majority of patients have preserved hearing. Mild developmental delay was reported in 7 patients, however, the 4 adults with AMS had normal development and intelligence. The oldest reported patient in the literature with AMS was a 46 year old woman. Most of the patients with AMS were born at term via normal vaginal delivery, and they had < 50% birth weight. Some AMS patients developed thin and fuzzy hair on their scalp, but they still had sparse eyebrows and eyelashes as adults, and their skin remained thin and wrinkled in appearance with visible blood vessels. Of the 17 reported cases, 2 patients had skin biopsies performed, both of which showed no abnormalities.

When presented with a patient with possible AMS, there are two syndromes with similar features: Barber-Say syndrome and FRAS-FREM complex disorders. Barber-Say syndrome is a rare congenital disorder that is similar to AMS and presents with redundant skin, abnormal ears, and macrostomia. Unlike AMS, patients with Barber-Say syndrome have generalized hypertrichosis and ectropion. No gene defect has been elucidated for Barber-Say syndrome. AMS also overlaps with FRAS-FREM complex disorders, which are composed of mutations in FRAS1, FREM2, or GRIP1 genes that play a role in epidermal-dermal interactions during embryonic development. This syndrome presents with ablepharon, alopecia, macrostomia, and syndactyly of the hands or feet. Schanze et al (2013) tested 11 patients with AMS for the FRAS-FREM gene mutations and found no mutations in these genes to suggest that AMS is a disease separate from FRAS-FREM complex disorders, rather than a spectrum of FRAS-FREM disorders.

Treatment of AMS includes prompt ophthalmologic management at birth with frequent ocular lubricants and antibiotics. In addition, prompt eyelid reconstruction and possible corneal replacements are needed to preserve visual function. Patients may also need cranio-facial reconstructive surgeries to correct their macrostomia and dysmorphic ears. While AMS patients have dry skin, there has been no association with ichthyosis in the literature. Further longitudinal research needs to be conducted to elucidate optimal management of the skin in patients with AMS. In addition, the actual genetic abnormality remains to be delineated in the future.

Essential Lessons:

- Ablepheron-macrostomia syndrome (AMS) is a rare congenital disorder consisting of absent eyelids, macrostomia, and skin findings including thin skin, alopecia or sparse hair on the scalp, absent eyelashes and eyebrows, and xerotic skin.
- It is important to provide immediate post-natal ocular management to prevent loss of vision.

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Cases Presented by Pauline Scott, MD
Sophie M. Worobec, MD and Maria Tsoukas, MD, PhD

Patient A

History of Present Illness:

This 24 year old African American male presented with a two month history of multiple draining skin lesions on the face, trunk, and lower extremities. In addition, he complained of persistent cough, hemoptysis, night sweats, and unintentional weight loss.

Past Medical and Surgical History:

None

Medications:

Lactobacillus, iron supplement

Allergies:

No known drug allergies

Social History:

The patient was unemployed with no recent travel outside of the United States, exposure to animals, soil, construction, or ill contacts. He smoked one to two cigarettes daily with occasional marijuana use.

Review of Systems:

The patient reported a 40-50 pound weight loss over the past two months, night sweats, persistent cough, and hemoptysis.

Physical Examination:

The patient had multiple verrucous plaques with purulent drainage and yellow-brown crust on the right frontal hairline, right parietal scalp, and left ear pinna. A few tender hyperpigmented nodules were located on the abdomen, left buttock, and right lateral knee. Two nodules with central ulceration, purulent drainage and yellow-brown crust were seen on the right thigh.

Laboratory Data:

The following were positive or abnormal:
Urine blastomyces antigen 0.49 ng/ml (positive), serum blastomyces antigen 0.39 ng/ml (positive), urine histoplasma antigen 0.58 ng/ml (positive), serum histoplasma antigen 0.57 ng/ml (positive), Quantiferon TB gold test indeterminate, white blood cell count 14.1 k/μl (3.9-12.0)

The following were negative or within normal limits:
HIV, syphilis, ACE, ANA, amylase, lipase

Diagnostic Procedures and Tests:

04/14 **Radiograph, chest:** The lungs show a segmental opacity at the medial right base with the remaining lungs clear.
04/14 **Computed tomography, chest:** There are tree-in-bud opacities in the right lower lobe surrounding an area of dense consolidation. The left lung is clear. There is no suspicious hilar, mediastinal,or axillary lymphadenopathy.
04/14 **Wound culture, abdomen:** coagulase negative Staphylococcus species
04/14 **Fungal culture, skin:** growth of *Blastomyces dermatitidis*
04/14 **Acid fast bacilli culture:** negative
04/14 **Bronchoalveolar lavage fungal culture:** few *Blastomyces dermatitidis*

Histopathology:
Abdomen, skin: There is a deep, folliculocentric, acute and chronic inflammatory infiltrate with rare multinucleated giant cells. Grocott's methenamine silver (GMS), Periodic-Acid Schiff (PAS), and Fite special stains are negative for fungal and acid-fast microorganisms. Subsequent levels with PAS stains were performed with no fungal elements identified.

Diagnosis:
Disseminated Blastomycosis

Treatment and Course:
The patient was started on IV liposomal amphotericin B for two weeks and then transitioned to PO itraconazole for a planned duration of six to twelve months with improvement in his skin nodules and systemic symptoms.

Patient B
History of Present Illness:
This 66-year-old African American male presented with a one month history of tender skin lesions on the scalp, left hand, right arm, and left foot. Prior to the skin lesions, he had noticed a persistent non-productive cough and increasing fatigue.

Past Medical and Surgical History:
Diabetes mellitus, hypertension, cerebrovascular accident, degenerative joint disease in left knee

Medications:
Metformin, insulin NPH, hydrochlorothiazide, nifedipine, aspirin, tramadol

Allergies:
Lisinopril

Social History:
The patient was a retired postal worker. He traveled to Wisconsin in 2013 and denied any exposure to ill contacts. He quit smoking five years ago and used alcohol occasionally.

Review of Systems:
The patient reported an ongoing non-productive cough and increasing fatigue. He denied weight loss, hemoptysis, and night sweats.

Physical Examination:
The patient had a 3 cm yellow, crusted verrucous plaque on the left frontal scalp. Two ulcerated violaceous plaques with central crust were noted on the left thenar eminence and right posterior forearm. One ulcerated violaceous papule with central crust was located on the left lateral foot.

Laboratory Data:
The following were negative or within normal limits:
Urine blastomyces antigen, urine histoplasma antigen, HIV, Quantiferon TB gold

Diagnostic Procedures and Tests:
04/14 **Radiograph, chest:** There is an approximately 4.7 x 4.8 cm left parahilar mass with peripheral spiculations extending superiorly and laterally towards the pleura. The remainder of the lungs are clear.
05/14 **Computed tomography, chest:** There is an area of consolidation in the anterior second left upper lobe with air bronchograms.
05/14 **Fungal culture, skin:** One colony of *blastomyces dermatitidis* isolated.
05/14 **Bronchoalveolar lavage:** Macrophages and other mononuclear inflammatory cells, bronchial, and squamous epithelial cells, and neutrophils present. No viral cytopathic changes or malignant cells identified.

05/14 **Bronchoalveolar lavage fungal culture**: No fungi isolated after four weeks.

Histopathology:
Left hand, skin: The epidermis shows reactive changes and hyperplasia. GMS and PAS stains are negative for fungal elements.

Transbronchial biopsy: Bronchial and alveolar tissue with noncaseating chronic granulomatous inflammation and microcalcification with giant cell host response. Negative for malignancy. GMS stain for fungi is negative. AFB stain is negative.

Diagnosis:
Disseminated Blastomycosis

Treatment and Course:
The patient was started on PO itraconazole that was then switched to oral voriconazole 200 mg twice daily as he developed dyspnea and lower extremity edema while on itraconazole. The patient was to receive six to twelve months of treatment and noted improvement in his skin lesions, cough, and fatigue.

Discussion:
North American blastomycosis, also known as Chicago disease, Gilchrist's disease and blastomycosis, is a systemic mycosis caused by the thermally dimorphic fungus *Blastomyces dermatitidis*. In North America, infection is endemic in the south central and Midwestern United States as well s Canada. Most identified cases have come from the Missouri, Ohio, and Mississippi River basins, and the Great Lakes areas in the United States and Quebec and the Maritime provinces in Canada. There have also been reported cases in Mexico, India, and Africa. It is found predominately in men, occurs most commonly in the fourth decade of life, and is infrequent in children. Risk factors for symptomatic disease include pre-existing disease. In one study, 22% of affected patients had diabetes mellitus. It is thought that men are more affected as a result of occupational or recreational activities that result in exposure to *B. dermatitidis* such as forestry, hunting, fishing, and other outdoor activities. Outdoor activity after periods of heavy rain are a risk factor for pulmonary involvement.

Infection is transmitted most commonly via inhalation of *B. dermatitidis* conidia. However, venereal (from men with prostatic involvement) as well as intrauterine exposure leading to infection has been documented. It has also been reported from the bite of a dog suffering from pulmonary blastomycosis. The conidia are formed in the mold phase which is found in warm, humid soil containing organic material. In the lungs, if the natural resistance from alveolar macrophages, monocytes, and neutrophils is overcome, the conidia then transform to the yeast phase and increase in number. The infection can then spread through lymphohematogenous dissemination to other organ systems such as the skin, bones, male genitourinary system, and the central nervous system.

Clinically, blastomycosis is grouped into two forms: pulmonary and extrapulmonary. The most common manifestations of pulmonary blastomycosis are weight loss, cough, cutaneous lesions, fever, thoracic pain, and hemoptysis. Patients can also remain asymptomatic or have very mild symptoms. In extrapulmonary or disseminated blastomycosis, the skin is the most frequently affected organ. Cutaneous lesions may be verrucous plaques with punctate areas of purulence, ulcers with raised borders, or painful subcutaneous nodules. In severe pulmonary infection, subcutaneous abscesses and fistulas may be seen. These lesions can be confused for other conditions such as keratoacanthoma, pyoderma gangrenosum, squamous cell or basal cell carcinomas, syphilis, cutaneous verrucous tuberculosis, granuloma inguinale, pemphigus vegetans, trichophytic granulomas, verrucous pyoderma, cryptococcosis ,chromomycosis, drug eruption, or iodide or bromide halogenodermas .

The classic histologic feature of blastomycosis is a pseudoepitheliomatous hyperplasia with dermal and epidermal neutrophil abscesses, and granulomatous formation. The 8-15 μm yeast organisms are broad-based with budding and have a refractory cell wall. They are best seen with Gomori's methenamine silver (GMS) or periodic acid-Schiff stains.

Other diagnostic testing includes *B. dermatitidis* antigen detection using human urine or serum. Positive test results usually occur when disseminated disease exists. There is cross reactivity associated with Histoplasma antigens. Direct microscopic examination with potassium hydroxide (KOH) solution can also be used on specimens such as skin scrapings, sputum, and purulent material from abscesses. Culture still remains the most sensitive test for detecting blastomycosis. Growth occurs after 5-10 days but may take longer if there are fewer yeast cells present.

Treatment of disseminated blastomycosis is contingent upon the severity of the disease. For moderately severe to severe disease, a lipid formulation of amphotericin B (3-5 mg/kg/day) or amphotericin B deoxycholate (0.7-1 mg/kg/day) is used for one to two weeks or until the patient improves. This is then transitioned to oral itraconazole 200 mg three times per day for three days then 200 mg twice per day for at least twelve months. For mild to moderate disease, oral itraconazole 200 mg three times per day for three days then 200 mg daily to twice per day is continued for six to twelve months. Less commonly used agents include ketoconazole, fluconazole, and voriconazole. Itraconazole has been shown to be more effective than ketoconazole in the treatment of non-CNS blastomycosis. Studies using fluconazole have been sparse but as it has exceptional penetration into the CNS, it may be studied more in the treatment of CNS blastomycosis. There are limited reports of the use of voriconazole, but it has been used in cases of refractory blastomycosis, CNS blastomycosis, and treatment of immunosuppressed patients. There are no reports of posaconazole use in blastomycosis treatment.

Essential Lessons:

- Blastomycosis is caused by the thermally dimorphic fungus *Blastomyces dermatitidis*.
- Disseminated blastomycosis is seen in approximately 25% of cases with skin being the most frequently affected organ.
- Treatment of this disease may take up to a year or longer depending on its severity.

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Case Presented by Amanda Marsch, MD
and Jane Scribner, MD

UNKNOWN CASE

This 77 year old male presented with papules on his distal extremities.

Case 10

Case Presented by Kimberly Jerdan, MD, Claudia Hernandez, MD and Milena Lyon, MD

History of Present Illness:
This 66 year old female presented with a 4 year history of pruritic, scaly and hyperpigmented lesions on her lower extremities. The patient had never been evaluated or treated for her condition prior to presentation.

Past Medical History:
Seizure disorder since age 12 and glaucoma

Medications:
Carbamezapine, travoprost eye drops, and timolol eye drops

Allergies:
No known drug allergies

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

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

Physical Examination:
The patient had diffuse thin, white scale with a sharp edge in arciform patterns. Within this background were several scattered hyperpigmented, dry, scaly patches on bilateral lower legs.

Laboratory Data, Diagnostic Procedures and Tests:
Systemic work-up, including electrocardiogram and chest radiograph are pending with her outside primary care physician.

Histopathology:
Right leg, skin: The epidermis demonstrates extensively compact hyperkeratosis with deep granulomatous infiltration into the subcutaneous tissue. Noncaseating "naked" granulomas are revealed at higher power, composed of epithelioid histiocytes and sparse surrounding lymphocytic inflammation. Conspicuous foreign body giant cells are present. Acid Fast Bacilli (AFB), Fite, and Periodic acid-Schiff (PAS) stains are negative for fungal or acid fast organisms.

Diagnosis:
Ichthyosiform sarcoidosis

Treatment and Course:
Pending results of a systemic work-up, the patient was initially treated with 0.05% fluocinonide ointment twice daily. Due to insurance restrictions, evaluation for systemic involvement is being performed by her primary care physician concerning possible lung, heart, and eye involvement.

Discussion:
Sarcoidosis is a granulomatous disease with multisystem involvement that may include cutaneous, pulmonary, ocular, and cardiac findings. Cutaneous lesions of sarcoidosis vary from most common nonspecific lesions of erythema nodosum to more specific lesions such as lupus pernio, infiltrated plaques, maculo-papular lesions, and subcutaneous nodules. Ichthyosiform sarcoidosis (also known as sarcoidosis with acquired ichthyosis) is an infrequent presentation of sarcoidosis with less than 25 reported cases.

Ichthyosiform Sarcoidosis (IS) presents as rhomboidal, adherent scaling on the lower extremities. It is believed to be an excellent marker for systemic disease, with 95% of reported cases having some form of internal involvement. All patients with ichthyosiform manifestations of sarcoidosis should undergo a thorough evaluation for systemic disease. Thus far IS has been described only in individuals with skin of color. The acquired ichthyosiform changes appear to precede the diagnosis of systemic disease in most cases by a median of 3 months; however it can occur simultaneously, or after, systemic disease diagnosis. Systemic therapy is often needed for this type of sarcoidosis since it has been reported to progress rapidly.

Proper recognition of IS is critical in the monitoring and treatment of sarcoidosis, as it may be a sign of organ involvement.

Treatment of IS depends on the amount of systemic involvement. IS lesions are often treated with topical corticosteroids. If refractory to topical steroids, IS patients may respond to oral prednisone or other common treatments such as hydroxychloroquine, methotrexate, or thalidomide.

Essential Lessons:

- Include sarcoidosis in the differential diagnosis of patients with acquired ichthyosis.
- Patients with IS are at high risk of systemic disease and should undergo a thorough evaluation.

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Case Presented by Eden Pappo, MD
and Iris K. Aronson, MD

History of Present Illness:
This 33 year old African-American female presented with a facial rash following type 1 diabetes-associated kidney and pancreatic transplants. The rash began two months prior to her presentation. She had been self-medicating with ketoconazole shampoo and cream that had been prescribed previously with no improvement. The rash was associated with loss of hair including eyebrows, eyelashes and axillary hairs with sparing of scalp hair. Her immunosuppression course included prednisone, azathioprine and tacrolimus as well as previous mycophenolate mofetil treatment.

Past Medical and Surgical History:
Type 1 diabetes, gastroesophageal reflux disease, kidney and pancreas transplants, chronic kidney disease

Medications:
Azathioprine, amlodipine, sevelamer, aspirin, ergocalciferol, gabapentin, lansoprazole, magnesium oxide, metoprolol, prednisone, and tacrolimus

Allergies:
Penicillin – urticaria

Physical Examination:
The patient's forehead, nose, medial cheeks and pinnae had diffuse, bilateral, pinpoint papules on a background of erythema. These papules were 2-5mm and had a central hyperkeratotic spiny projection. Her upper eyelids and nose had diffuse follicular, white, spiny projections. Her eyelashes, eyebrows and bilateral axillae had markedly reduced hair density. The scalp lacked erythema, scale, and any similar lesions to those seen on the face.

Laboratory Data, Diagnostic Procedures and Tests:
None

Histopathology:
Face, skin: There is a dilated and dystrophic hair follicle with infundibular orthohyperkeratosis. The follicle shows abnormal maturation with prominent inner root sheath differentiation and lacks a fully formed papillae; no hair shaft is seen. The cells have prominent eosinophilic cytoplasm and contain numerous trichohyaline granules. Eosinophilic intraepithelial viral inclusions are also observed.

Diagnosis:
Trichodysplasia of Immunosuppression

Treatment and Course:
The patient's original treatment prescribed by the dermatology department, guided by case reports in the literature, included metronidazole cream daily as well as a trial of topical tretinoin. Neither treatment resulted in clinical improvement. Shortly after the dermatologic diagnosis was established, the patient's transplant surgeon stopped azathioprine, decreased the tacrolimus dose, and restarted mycophenolate mofetil. These alterations led to a mild improvement in her skin findings. The patient was also prescribed topical cidofovir 1% daily based on its efficacy per literature review. Treatment would require the oncology pharmacy to compound the antiviral medication. Unfortunately, insurance did not approve cidofovir.

Discussion:
Trichodysplasia of immunosuppression (TOI) is a cutaneous eruption consisting of follicular papules that can lead to scarring facial alopecia. TOI is primarily observed in immunosuppressed patients, particularly kidney, pancreas and heart transplant recipients, first identified clinically in 2010. It may also occur in

patients with hematologic malignancies such as leukemia and lymphoma, and has recently been associated with lupus. Overall much of the literature is presented in the form of case reports. TOI is likely the same clinical entity as viral-associated trichodysplasia spinulosa, trichodysplasia spinulosis and cyclosporine-induced folliculitis. Clinically, it affects the central face causing follicular papules and keratin spines as well as a scarring alopecia of the eyebrows and facial hair. The lesions may be asymptomatic or pruritic. As the disease progresses, the scarring of the ears, nose, and eyebrows can be disfiguring. Hair loss is secondary to spine-like concretions that replace the hairs within the follicles.

Diagnosis is mainly based on clinical presentation, however biopsies confirm the diagnosis. Viral inclusions showing trichodysplasia spinulosa-associated polyomavirus (TSPyV) in the inner root sheath cells may be identified on formalin-fixed paraffin-embedded biopsies with transmission electron microscopy. Standard histopathology of the inner root sheath cells may demonstrate enlarged, dystrophic hair follicles with prominent eosinophilic, perinuclear globules, often without a hair shaft. Intraepithelial viral inclusions can also be seen. Polyomavirus-specific immunohistochemical staining and PCR for the poylomavirus-specific DNA may also be performed to confirm the diagnosis. TSPyV has been detected in the urine of a renal transplant patient with TOI as well, which may offer a non-invasive diagnostic option.

The mainstay of treatment includes reduction of immunosuppression, as demonstrated effectively in this case, and antiviral therapy. Topical cidofovir (cream or ointment, one to three percent) has been particularly effective; additional options include topical acyclovir, oral or topical retinoids, and oral valganciclovir.

Essential Lessons:

- Trichodysplasia of immunosuppression is a follicular and papular condition affecting the face with resulting alopecia and potential disfigurement.
- TOI is associated with polyomavirus and viral detection along with histopathology supports the clinical diagnosis.
- The most effective treatments include reduction in immunosuppression and topical cidofovir.

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