Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, April 17, 2019
Gleacher Center – Chicago, IL

Conference Host:

COOK COUNTY HEALTH & HOSPITALS SYSTEM
CCHHS

Stroger Hospital of Cook County
Division of Dermatology
Chicago, Illinois

Program

Host: Stroger Hospital of Cook County
Wednesday, April 17, 2019
Gleacher Center, Chicago

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *All activities will take place on the 6th Floor of the Gleacher Center*
8:30 a.m. - 10:15 a.m.	**Clinical Rounds** Slide viewing/posters
9:00 a.m. - 10:00 a.m.	**Basic Science/Residents Lecture** "Tracking the Arc of Treatment Options in Pemphigus: From General to Increasingly Targeted Therapies" *Animesh A. Sinha, MD, PhD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:15 p.m.	**Resident Case Presentations & Discussion; MOC Self-Assessment Questions**
12:15 p.m. - 12:45 p.m.	**Box Lunches & visit with exhibitors**
12:55 p.m. - 1:00 p.m.	**CDS Business Meeting**
1:00 p.m. - 2:00 p.m.	**General Session** BARSKY LECTURE - "Rethinking Pemphigus: How New Insights are Disrupting our Understanding of and Approach to Complex Disease" *Animesh A. Sinha, MD, PhD*
2:00 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS monthly meeting – Hosted by Rush University
Wednesday, May 1st; Gleacher Center, Chicago

IDS/CDS Joint Conference & Awards Luncheon
Wednesday, June 5, 2019; Stephens Convention Center, Rosemont

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

Guest Speaker

ANIMESH A. SINHA, MD, PHD

Rita M. and Ralph T. Behling Professor of Dermatology, Department of Dermatology
University at Buffalo
Buffalo, New York

Animesh A. Sinha, MD, PhD has been a member of the faculty at the University at Buffalo since 2011, where he also served as chair of the Department of Dermatology from 2011 to 2017. He now holds the Rita M. and Ralph T. Behling Endowed Chair with University Tenure. Dr. Sinha also holds adjunct faculty appointments in biochemistry, microbiology and immunology at the University at Buffalo.

Dr. Sinha earned his medical degree at the University of Alberta, Edmonton, in 1982 and a PhD in Immunology at the same institution in 1986. He engaged in a research fellowship in immunology at Stanford University from 1986 to 1992. Dermatology residencies were completed at the University of Alberta, Edmonton, in 1995 and at Yale University, New Haven, CT, in 1998. Dr. Sinha is a Certified Medical Educator having completed the UB/Royal College of Physicians course at the University at Buffalo in 2015.

His research interests involve immunological tolerance and autoimmunity - to pinpoint targets for immune intervention and potentially gene therapy in autoimmune disease. Dr. Sinha has numerous research projects, publications and other recognitions to his credit.

CME Information

4.17.2019

This educational activity is jointly provided by the Chicago Dermatological Society in partnership with the Indiana Academy of Ophthalmology.

Overview

The Chicago Dermatological Society was established in 1901 and has strived to provide meaningful educational opportunities to dermatologists in the Chicago area for more than a century. Guest speakers from across the country share their expertise with CDS members, as well as residents in training medical students doing their dermatology rotation. CDS schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. In addition to two lectures given by the guest speaker, the residents of the host institution present cases which are offered for audience discussion. In addition, live patients, posters and microscopic slides prepared by the residents are made available during the "clinical rounds" portion of the meeting. CDS also offers a session that qualifies for "Maintenance of Certification" self-assessment questions under the auspices of the American Board of Dermatology.

Target Audience

This activity has been designed to meet the educational needs of dermatologists. CDS members, residents in training and medical students engaged in their dermatology rotation are invited to attend.

Learning Objectives

At the conclusion of the 2018/19 series of meetings, the participant should be able to:

1. Discuss key factors in the diagnosis and treatment for various diseases and conditions of the skin, including use of new or emerging medication options.
2. Describe the surgical techniques for treatment of skin cancers and for cosmetic purposes.
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 is planned and implemented by Indiana Academy of Ophthalmology (IAO) and the Chicago Dermatological Society. IAO is accredited by the Indiana State Medical Association to provide continuing education for physicians.

Credit Designation for Physicians – IAO designates this live activity for a maximum of 4.75 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendees are required to submit a CME claim form upon departure from the conference. Please leave your form, along with the evaluation form, at the registration table when you leave the meeting. Thank you for your attention to this important item.

Disclosure of Conflicts of Interest

The IAO and CDS require instructors, planners, managers and other individuals and their spouse/life partner who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by IAO and CDS for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All speakers are asked to follow the "first slide" rule to repeat their conflict of interest disclosures during their talk.

Neither the guest speaker, Animesh A. Sinha, MD PhD, nor any members of the planning committee have any relevant conflicts of interest to disclose.

Continued next page

Contact Information

For information about the physician accreditation of this program please contact the CDS administrative office at: 847-680-1666; email: Rich@RichardPaulAssociates.com

Americans with Disabilities Act

In compliance with the Americans with Disabilities Act, we will make every reasonable effort to accommodate your request. For any special requests, contact CDS at: Rich@RichardPaulAssociates.com

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Dislosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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*Protocol to be posted same-day on the CDS website

Key location(s): generalized **CASE 1A**

Presented by Rahil Dharia MD, and Warren Piette MD

History of Present Illness

A 54-year-old male presented with a four-week history of a pruritic blistering rash on his chest, back, upper extremities, and oral mucosa. Two weeks prior, the patient was treated in the emergency room with a 1-week course of doxycycline 100 mg BID with no improvement. Patient endorsed significant pruritus and odynophagia.

Past Medical History

None

Medications

None

Allergies

NKDA

Social History

Non-contributory

Review of Systems

Negative for fever, chills, cough, arthralgias, pain with urination or defecation, eye pain, blurry vision, abdominal pain, nausea, vomiting, diarrhea, headache, or additional skin lesions

Physical Exam

Vertex scalp and nose:	Few scattered erythematous crusted papules
Trunk and extremities:	Scattered superficial small erosions, some with central hemorrhagic crust; scattered erythematous edematous papules with central erosion or crust, scattered intact vesicles, some on an erythematous base
Medial aspect of feet:	Larger intact tense bulla with erythematous border

Laboratory Data

The following labs were remarkable/abnormal:

HIV	Nonreactive
HSV1 PCR DNA	Negative
HSV2 PCR DNA	Negative
HSV/VZV PCR DNA	Negative

Histopathology

Punch biopsy, left upper arm: suprabasilar clefting

Direct immunofluorescence, left upper arm: there is linear/granular IgG deposition throughout the epithelial cell surfaces. There are also linear/granular C3 deposits on the lower two-thirds of

the epithelial strata. There are no immunoreactants at the basement membrane zone and no IgA, IgM, C5b-9 or fibrinogen deposits seen in this specimen.

Radiology
CT, chest: No lymphadenopathy within the chest, abdomen, or pelvis. Nonspecific soft tissue prominence along the right posterior aspect of the trachea, at the level of the thoracic inlet.

Chest AP Portable: No acute cardiopulmonary pathology

Diagnosis
Pemphigus vulgaris

Treatment and Course
The patient was initially treated with prednisone ranging from 50-60 mg. Prednisone was unable to control his disease and his elevated blood pressure restricted the ability to increase the dosage. The patient was admitted multiple times for IV methylprednisolone 500 mg daily and strict blood pressure monitoring. After each discharge, the patient flared on maintenance prednisone. He received two rituximab 1000 mg infusions and was started on mycophenolate mofetil 1000 mg BID. The patient improved after his second infusion and is currently doing well on prednisone 30 mg and mycophenolate mofetil 500 mg BID.

Key location(s): generalized **CASE 1B**

History of Present Illness
A 44-year-old female presented with a six-week history of a widespread pruritic blistering rash. The lesions began on the legs and spread to the arms. The only new medication prior to onset were two leuprolide injections.

Past Medical History
Hypertension

Medications
Metoprolol XL, leuprolide

Allergies
None/NKDA

Social History
Non-contributory

Review of Systems
Negative for fever, chills, weight change, fatigue, arthralgias, or additional skin lesions

Physical Exam

Trunk and extremities:	many edematous erythematous plaques with tense bullae within, multiple arranged in an annular "string of pearls" configuration

Histopathology
Punch biopsy, left arm: Subepidermal bullous dermatosis with mild superficial perivascular lymphocytic infiltrate and some eosinophils

Direct immunofluorescence, left arm: positive for bullous pemphigoid

Diagnosis
Bullous pemphigoid

Treatment and Course
The patient was originally treated with methotrexate and prednisone ranging from 60-100 mg without much improvement. She underwent IVIG therapy and was started on rituximab 1000 mg infusions. Each time her maintenance prednisone was tapered, she began to flare with new lesions. Patient underwent a total of 10 rounds of rituximab infusions. She is currently doing well on methotrexate 15 mg weekly and has tapered off of prednisone

Discussion
Pemphigus vulgaris (PV) is a mucocutaneous autoimmune bullous disorder of the skin and mucous membranes that commonly occurs in the fifth to sixth decades of life. Seventy to eighty percent of all patients with pemphigus have the vulgaris type, which is characterized by autoantibodies against intercellular desmoglein-3. PV is a potentially life-threatening autoimmune mucocutaneous disease with a mortality rate of approximately 5-15%.

Patients with PV have oral lesions 50-70% of the time. Mucosal lesions may precede cutaneous lesions by weeks or months. The classic cutaneous finding is a flaccid blister that is fragile and

produces painful erosions. The diagnosis of PV is made via biopsy for hematoxylin and eosin (H&E) of involved skin and direct immunofluorescence (DIF) of perilesional skin. H&E with suprabasilar acantholysis and blister development is suggestive of PV and IgG and C3 deposition binding to the cell surface on DIF confirms the diagnosis.

The primary therapy for patients with PV has been corticosteroids. Prior to steroid development in the early 1950s, the death rate was >90%, compared to 10% currently. However, the high dose and duration of corticosteroids can lead to numerous adverse effects. Given this, adjuvant immunosuppressive therapy should be considered early in the treatment course. These agents include azathioprine, cyclophosphamide, mycophenolate mofetil, and IVIG. In addition, rituximab is an anti-CD20 biologic agent that has emerged as a promising therapy for moderate to severe pemphigus that can induce remission as early as 1-3 months. Recent evidence suggests better outcomes when rituximab is used as a first-line agent, leading to FDA approval for Rituximab as a first line agent in 2018.

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal bullous skin disorder. BP most commonly occurs in the fifth to seventh decades of life. Generally presenting as widespread tense blisters with significant pruritus, BP is characterized by immunoglobulin G autoantibodies that bind to the hemidesmosome, specifically BP230 and BP180.

Diagnosis is established via histopathology of the edge of a blister and direct immunofluorescence (DIF) of perilesional skin. If the DIF is positive, indirect immunofluorescence (IDIF) can be performed. DIF studies usually reveal IgG and C3 deposition in a linear band at the dermal-epidermal junction. IDIF of the patient's serum reveals IgG on the blister roof in patients with BP.

The therapeutic goal is to stop the formation of new blisters as well as promote healing of current blisters and erosions. The most commonly used medications are anti-inflammatory agents (e.g. corticosteroids, tetracyclines, dapsone) and immunosuppressants (e.g. azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, IVIG). For recalcitrant disease that is difficult to control, rituximab is an anti-CD20 antibody that has been shown to be effective for the treatment of therapy-resistant BP.

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Key location(s): left chest wall **CASE 2**

Presented by Maria Yaldo MD, David C. Reid, and Jerry Feldman MD

History of Present Illness
A 58-year-old man presented with an ulcerated plaque on the left chest wall which began as a "pimple" one year prior. The lesion had intermittent serosanguinous drainage, and it was minimally painful. He had received no previous treatment.

Past Medical History
None

Medications
None

Social History
Tobacco use, ½ PPD
Drinks alcohol daily
No illicit drug uses

Family History
Brother – lung cancer at age 50
Brother – prostate cancer at age 60

Review of Systems
Negative for fever, weight loss, fatigue, shortness of breath, cough, hemoptysis, hematuria, and hematochezia

Physical Exam

Non-skin:	Vital signs were normal
Skin:	Left chest: 5 x 4cm ulcerated friable tumor with firm, hyperpigmented to pink borders obliterating the nipple and minimal serous drainage
Lymph nodes:	Left axillary lymphadenopathy present

Histopathology
Left chest, punch biopsy: Diffuse tubular aggregates of poorly differentiated neoplastic cells extending into the deep dermis. Immunohistochemical staining positive for CK7 and GATA-3, negative for CK-20, TTF-1/NapsinA, CDX-2, p63, and PSA

Radiology
CT, chest: left chest wall mass with associated enlarged left axillary lymph nodes. Multiple pulmonary nodules with additional multiple lytic and sclerotic bony lesions concerning for metastatic disease.
CT, abdomen/pelvis: enlarged left inguinal lymph nodes
CT, head: no evidence of intracranial metastatic disease

Diagnosis
Metastatic breast cancer

Treatment and Course
The patient was referred to medical oncology; however, he decided to pursue care back in his

hometown in Louisiana.

Discussion

Male breast cancer is rare, accounting for only 1% of breast cancer diagnoses in the United States, and less than 0.1% of cancer-related deaths in men. Risk factors include first-degree relatives with breast cancer, age, exposure to exogenous estrogens, and obesity. In contrast to women, men tend to present at later stages likely due to a delay in diagnosis. In general, cutaneous manifestations of breast cancer occur in approximately 30% of cases. About 3% of breast cancer cases initially present with cutaneous manifestations.

The majority of cases of male breast cancer present with a palpable subareolar mass. Less often, nipple retraction, ulceration, discharge, and bleeding may be the presenting signs. In one review, cutaneous involvement in male breast cancers commonly presented as vegetative plaques that involved the nipple or areola as seen in our patient. This presentation is likely due to contiguous spread as breast epithelium in men is limited to large ducts near the areola.

Tumors may also spread to the skin via a lymphatic or hematogenous route often leading to in-transit or metastatic disease. Breast cancer is the most common internal malignancy to metastasize to the skin in women, whereas lung cancer is the most common in men. Cutaneous metastatic breast cancer commonly involves the anterior chest wall or the site of mastectomy in over 75% of cases. The most common presenting lesions are dermal or subcutaneous nodules found in approximately 80% of patients. The nodules are often skin colored, firm, non-tender, round or oval, and mobile. They can be solitary or multiple and may ulcerate. Other less frequent manifestations of cutaneous breast cancer include carcinoma telangiectodes (8-11%), carcinoma erysipeloides (3-6.3%), carcinoma en cuirasse (3-4%), and alopecia neoplastica (2-12%). Carcinoma telangiectodes presents with purpuric papules, nodules, or plaques that are often pruritic. Histologically, atypical tumor cells within dilated vascular channels are seen. Carcinoma erysipeloides, also known as inflammatory metastatic carcinoma, is characterized by warm, tender, plaques or patches similar to erysipelas. Pathology of this type shows tumor invasion of dermal lymphatics. Carcinoma en cuirasse appears as a firm, indurated, erythematous plaque that may have a peau d'orange appearance. The pathology displays dense fibrosis and few neoplastic cells that may have single file pattern. Alopecia neoplastica presents with circular, smooth, indurated areas of alopecia that may mimic alopecia areata.

Immunohistochemical staining of breast cancer is positive for cytokeratin 7 in two-thirds of cases. Other positive markers include gross cystic disease fluid protein 15, GATA3, estrogen receptor (ER), progesterone receptor (PR). ER and PR are positive in about half of the cases in general, although about 90% of male breast cancers are hormone receptor positive. Other stains that may be positive, but less specific include carcinoembryonic antigen, E-cadherin, Ber-EP4, and rarely S100. Breast cancer is usually negative for cytokeratin 20, cytokeratin 5/6, and thyroid transcription factor-1, which helps rule out other malignancies.

Treatment of cutaneous metastatic breast lesions includes surgical excision or radiotherapy to symptomatic lesions for palliative relief. The use of cryotherapy along with either topical imiquimod or topical fluorouracil 5% has been reported with improvement in cutaneous lesions. In addition, a recent phase 2 clinical trial evaluated the use of topical imiquimod plus albumin bound paclitaxel for cutaneous lesions and found efficacy in disease regression. Responses, however, were short-lived.

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CASE 3

Presented by Dorothy Rodenbeck MD, MHS, and Warren Piette MD

A 63-year-old woman was admitted for work-up of acute altered mental status. The dermatology service was consulted for a diffuse asymptomatic rash that had been present for 2½ weeks.

UNKNOWN

CASE 4

Presented by Charles Vainder MD, and Vidya Shivakumar MD

A 70-year-old man presented with a four-year history of pruritic papules on his trunk and arms which acutely worsened four weeks prior to presentation.

UNKNOWN

Key location: right forearm **CASE 5**

Presented by Evan Stokar MD, and Shilpa Mehta MD

History of Present Illness
A 29-year-old man with a history of ulcerative colitis presented with an eroded nodule on his right forearm of 6 months' duration. The lesion was painful and bled with manipulation. He denied trauma prior to onset, new medications, recent illness, or similar lesions elsewhere.

Review of Systems
Positive for nausea, abdominal pain, hematochezia, weight loss
Negative for fever, chills, night sweats, fatigue, other skin lesions

Past Medical History
Ulcerative colitis

Medications
Prednisone, adalimumab, meselamine, tramadol

Social History
Positive for alcohol socially, negative for tobacco and illicit drug use
Works in IT industry

Physical Exam

General:	Well appearing, no acute distress
Skin:	Right forearm with a single 1cm pink, firm nodule with a central hemorrhagic erosion
Lymph nodes:	No palpable lymphadenopathy

Laboratory Data
CBC w/ diff, CMP, HIV, hepatitis panel, ANA, serum immunofixation studies all unremarkable

Radiology
CT with contrast, chest/abdomen/pelvis: unremarkable, no adenopathy

Histopathology
Shave biopsy, right forearm: nodular dermal infiltrate composed of sheets of histiocytes admixed with lymphocytes, plasma cells, neutrophils, and eosinophils. Evidence of emperipolesis and no cellular atypia. Immunohistochemical staining for S-100, CD68, and CD163 were positive. Factor XIIIa and CD1a were negative.

Diagnosis
Cutaneous Rosai-Dorfman disease

Treatment and Course
A full body skin exam was performed, which revealed no evidence of lymphadenopathy or other skin lesions. The patient was referred to hematology/oncology service and work-up for systemic disease was negative. The biopsy site was excised and showed no residual histiocytic proliferation. The patient continues to follow-up with dermatology and has no evidence of cutaneous recurrence or disease progression.

Discussion

Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytosis characterized by accumulation of activated histiocytes within various sites. RDD has a wide range of clinical phenotypes occurring in isolation or in the setting of malignancy and autoimmune diseases. Classically, patients present with bilateral cervical lymphadenopathy, but 43% of patients can present with extranodal disease. The prevalence is 1:200,000 and an estimated 100 new cases are reported in the United States per year. It is more frequently seen in children and young adults.

The etiology of RDD is not well understood. Viral etiologies such as herpes virus, Epstein-Barr virus, cytomegalovirus, and HIV are implicated, although a clear link has not been proven. The immunophenotype of RDD histiocytes is characterized by S-100 and CD68 positivity with variable CD163 and CD14 positivity. The cells are CD1a and CD207 negative.

The skin is involved in 10% of extranodal RDD cases and isolated cutaneous disease is rare. In cutaneous RDD, any skin site may be affected, with the face being most common. Lesions are typically slow-growing, painless, non-pruritic nodules and plaques varying from red to brown in color. Patients commonly present with multiple lesions in a bilateral distribution. Common clinical differential diagnoses include sarcoidosis, lymphoma, or other infiltrative processes. Rarely, patients present with acneiform lesions, large annular plaques resembling granuloma annulare, or palpable purpura mimicking vasculitis. Surgical excision is curative for unifocal disease and is the most effective treatment for solitary cutaneous disease compared to other methods such as local radiation or intralesional kenalog injections.

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CASE 6

Presented by Susan Hwang MD, and Joerg Albrecht MD

A 36-year-old man presented with a 6-month history of asymptomatic skin lesions which began around the mouth then generalized to involve the neck, torso and extremities.

UNKNOWN

Key locations: palms, soles, elbows, knees **CASE 7**

Presented by Jessika Davis MD, and David C. Reid MD

History of Present Illness
A 53-year-old Mexican woman presented with nail changes and worsening pain of her palms and soles secondary to skin lesions which had been present since birth. She reported similar skin findings and loss of all permanent teeth during childhood in herself and her two brothers. Her two sisters were unaffected.

Past Medical History
Ductal carcinoma in situ (diagnosed at age 51), duodenal neuroendocrine tumor (diagnosed at age 52), primary biliary cirrhosis (diagnosed at age 52), and hypertension.
Genetic testing (CancerNext-Expanded) for genes including MEN1, RET, and BRCA prior to presentation was negative.

Medications
Ursodiol, anastrozole, pantoprazole, losartan

Review of Systems
Negative for pyrexia, hearing impairment, history of skin or soft tissue infections, slow/sparse hair growth, hyperhidrosis, and known parental consanguinity

Physical Exam
Palmar hands: exaggerated skin lines and hyperkeratosis with pinpoint depressions; erythema and hyperkeratosis extending to the dorsolateral fingers and over the knuckles
Fingernails: convex curvature with horizontal grooving
Plantar feet: well demarcated erythematous plaques extending over the Achilles tendon with waxy yellow plates of scale over the forefoot and heel
Knees and elbows: pink, slightly scaly thin plaques with exaggerated skin lines
Malar cheeks: patchy erythema
Intraoral: edentulous

Laboratory Data
Pathogenic variant of the CTSC (cathepsin C) gene: positive for c.1141delC
variant p.Leu381SerfsX13

Imaging
Hand x-rays: joint spaces maintained, no evidence of acroosteolysis
Foot x-rays: no evidence of pes planus or acroosteolysis

Diagnosis
Papillon-Lefèvre syndrome

Treatment and Course
Given the patient's underlying liver disease, conservative management with topical therapy was initiated. She was treated with urea 40% cream, tazarotene 0.05% cream and petroleum jelly with minimal improvement. After discussion with her gastroenterologist, she began a trial of low dose acitretin 10 mg daily, which resulted in rapid symptomatic and clinical improvement of her skin lesions. After one month of acitretin, the patient reported being able to perceive light touch with her hands for the first time she could remember.

Discussion

Papillon-Lefèvre syndrome (PLS), also known as keratosis palmoplantaris with periodontopathy, is a rare genodermatoses characterized by palmoplantar keratoderma (PPK) and severe periodontitis resulting in premature loss of both primary and secondary dentition. It was first described in 1924, and since then, greater than 200 cases have been reported, and the associated gene has been elucidated.

Cutaneous manifestations of PLS begin prior to age five, typically within the first year of life. Patients develop symmetric, erythematous, hyperkeratotic palmoplantar plaques that are usually diffuse but have also been reported to be punctate, pitted, or honeycomb-like and may be associated with malodorous hyperhidrosis. The PPK is characteristically transgredient, as it is not confined to the palmoplantar surface and may extend to the lateral and dorsal aspects, including over the malleoli and Achilles tendons. Hyperkeratotic plaques resembling psoriasis can also be seen over the knees and elbows and may progress to involve the extensor extremities. Onychodystrophy may also be present including mild onychauxis, horizontal ridging, and convex curvature.

Other features of PLS include aggressive periodontal disease, increased susceptibility to infection, and asymptomatic ectopic intracranial calcification. Gingival tissue becomes inflamed after eruption of the deciduous teeth leading to hypermobility, drifting, and premature loss of teeth. The gingivae return to normal appearance after loss of the deciduous teeth; however, the cycle repeats itself after eruption of the permanent teeth. Patients may experience pain, halitosis, and regional lymphadenopathy, and many become edentulous by their early teens. In addition, approximately 20% of patients have recurrent pyogenic infections, although this may be underreported. The most common infections encountered are furuncles and skin abscesses; non-cutaneous infections include liver abscesses and pneumonia.

PLS is inherited in an autosomal recessive manner and approximately one-third of cases are attributed to parental consanguinity. It is caused by loss-of-function mutations in the cathepsin C (CTSC) gene, which encodes a highly conserved lysosomal protease. Over 75 mutations have been identified, and more than 50% are reported to be homozygous, which correlates to the high prevalence of consanguinity. Cathepsin C, also known as dipeptidyl peptidase 1, is a ubiquitous enzyme that is highly expressed in the lungs, kidneys, placenta, and immune cells, as well as in epithelial regions affected by PLS. It activates pro-inflammatory serine proteases that play a role in phagocytosis and chemotaxis, which may explain why some patients with PLS have increased susceptibility to infections. Cathepsin C has also been proposed to play a role in maintenance and integrity of the epidermis, although its exact role in PPK is unclear. Haim-Munk syndrome, considered by some to be a phenotypic variant of PLS, is also caused by mutations in cathepsin C. It presents similarly to PLS with the addition of arachnodactyly, acroosteolysis, onychogryphosis, and pes planus.

Management of PLS involves a multidisciplinary approach. Skin lesions may be treated with emollients, keratolytics, and systemic retinoids. Dental treatment includes good oral hygiene, antibiotics, chlorhexidine mouth rinse, and tooth extraction. Unfortunately, the periodontal disease responds poorly to treatment.

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Key location(s): generalized **CASE 8**

Presented by Morgan Covington MD, and David Reid MD

History of Present Illness
An 11-year-old girl, who recently immigrated from India, presented with a diffuse rash involving the neck, hands, elbows, back, and feet in association with arthralgias. She had a history of similar eruptions occurring intermittently since age 3. She was in the <5th percentile for height and weight. A previous biopsy done 9 years prior was consistent with pustular psoriasis. The patient was being treated with homeopathic creams and pills on presentation.

Medications
Herbal ointments

Review of Systems
Positive for joint pain, stiffness, decreased activity, poor appetite
Negative for fevers, chills, night sweats, recent illness, sore throat, GI complaints

Physical Exam

Vitals:	Temperature 102.7 Heart Rate: 142 (60-110) Blood pressure: 95/54 (102-120/60-75)
Skin:	Face and upper chest with hyperpigmented macules and patches with light brown scale Oral mucosa with fissured tongue Abdomen and back with thicker brown scale with underlying erythema Arms and legs with numerous pustules, some coalescing, and thick brown scale with underlying erythema

Laboratory Data
The following labs were remarkable/abnormal:

ESR	38	[0-11]
CRP	2.54	[0-0. 5]
IL-36rn gene analysis	Homozygous c.398_413del (p.Leu133Argfs*34)	

Diagnosis
Deficiency in interleukin (IL)-36 receptor antagonist (DITRA)

Treatment and Course
The patient was initially treated with cyclosporine 3mg/kg/day BID, intravenous fluids, and acetaminophen for pain control. Her condition improved quickly, and she was discharged three days after admission on cyclosporine and topical steroids with follow up appointments with dermatology, pediatric rheumatology, and pediatric ophthalmology. One and half months after discharge, she was started on subcutaneous injections of adalimumab 40mg every two weeks and cyclosporine was slowly tapered, then discontinued. Given the patient's history of recurrent severe generalized pustular psoriasis, deficiency in interleukin (IL)-36 receptor antagonist (DITRA) was suspected. Genetic testing revealed the presence of a previously unreported IL-36 receptor

antagonist gene (IL-36rn) mutation, homozygous c.398_413del (p.Leu133Argfs*34), thus confirming the diagnosis of DITRA. She continues to improve, with no new lesions or joint pain, on adalimumab.

Discussion

DITRA is a monogenic autoinflammatory disease due to mutations in the IL-36 antagonist gene (IL-36rn) resulting in dysfunctional IL-36 receptor antagonist (IL-36a). IL-36a is a part of the IL-1 family of cytokines. Its primary role is to antagonize proinflammatory cytokines IL-36α, IL-36β, and Il-36γ at the IL-36 receptor (IL-36R). By binding IL-36R, IL-36a prevents the downstream signaling of the nuclear factor-κB (NF-κB) and mitogen activated protein kinase (MAPK) proinflammatory pathways. Due to more prominent IL-36 expression in epithelial cells, DITRA has more severe skin findings when compared to other autoinflammatory conditions. Deficiency of IL-1 receptor antagonist (DIRA) is another closely related condition that also affects the IL-1 cytokine family. It shares features of DITRA including fevers, pustular eruptions, and elevated acute phase reactants. However, IL-1 receptors are expressed throughout the body, resulting in more systemic consequences, including osteomyelitis and periostitis.

Over 20 IL-36rn mutations have been reported in either homozygous, compound heterozygous, or heterozygous states. Regional variation has been described with the following mutations being more common in their respective populations: c.115+6T>C (p.Arg10Argfs*1) in Asia, c.338C>T (p.Ser113Leu) in Europe, and c.80T>C (p.Leu27Pro) in Africa. The case presented revealed an unreported mutation c.398_413del (p.Leu133Argfs*34). This mutation, like the previously reported c.420_426del (p.Gly141Metfs*29), is theorized to cause a frameshift mutation resulting in a premature stop codon and a truncated protein that poorly interacts with its target receptor.

Most cases of DITRA have childhood onset, though an adult-onset variant has also been reported. DITRA is characterized by severe, recurrent episodes of generalized pustular eruptions with erythema and scaling, high grade fever, asthenia, leukocytosis with neutrophilia, and elevated erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP). Gastrointestinal manifestations such as cholangitis, nausea, diarrhea, and mild gastric ulcers have also been reported. Flares may be medication-induced or triggered by infection, treatment withdrawal, menstruation, pregnancy, or stress.

DITRA has been treated with several regimens, with varying success. Efficacious treatment with acitretin, anakinra, etanercept, infliximab, adalimumab, secukinumab, ustekinumab, methotrexate, cyclosporine, and granulocyte and monocyte adsorption apheresis have been reported in the literature. In our case, adalimumab was the treatment of choice after starting cyclosporine due to the patient's initial complaint of arthralgias. Her arthralgias resolved completely within weeks of starting adalimumab.

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Key location(s): face **CASE 9**

Presented by Allison Wang MD, and Kubinne Kim MD

History of Present Illness
A 36-year-old man with no significant medical history presented to the emergency room with a 6-week history of productive cough and a 5-day history of a rash on the face. He developed worsening shortness of breath, fever, chills, and a 5-pound weight loss in the preceding two weeks. Because the lesions on his face were asymptomatic, he did not try any treatments.

Past Medical History
None

Medications
None

Social History
Denies tobacco, alcohol, or other drug use
Sexually inactive for one year. Previously only with female partners.
Works as a construction worker in Chicago and recently traveled to Alabama

Review of Systems
Positive for productive cough, shortness of breath, fever, chills, 5lb weight loss, fatigue, night sweats

Physical Exam

Non-skin:	T: 102.2 HR 125 bmp BP 110/70 RR 20/min O2 Saturation 97% RA NAD, AOx3
Skin:	Forehead, upper cutaneous lip, chin with about 15 erythematous papules, and a few with an umbilicated appearance

Laboratory Data
The following labs were remarkable/abnormal:

HIV1/2 antibody screen	Positive
HIV RNA quantitative	211449 copies/ml
CD4	7 cells/uL

Histopathology
Right temple, punch biopsy: mixed dermal infiltrate of neutrophils, lymphocytes, histiocytes, and necrosis. Associated with numerous small narrow-budding yeast. GMS and PAS stains highlight the fungal elements. Acid fast bacili, giemsa, and gram stain were negative.

Microbiology
Urine histoplasmosis antigen: positive

Sputum, fungal culture: positive for *Histoplasma capsulatum*

Radiology
CXR: extensive opacities within both lungs results in a miliary pattern.

Diagnosis
Disseminated Histoplasmosis

Treatment and Course
The patient was treated with amphotericin B for one week then transitioned to itraconazole until CD4 count reached greater than 100.

Discussion
Histoplasmosis capsulatum is a dimorphic fungus that causes opportunistic infections in immunocompromised individuals. In the United States, it is most prevalent in the Mississippi and Ohio river valley. It is acquired through inhaling microconidia from soil contaminated with bird or bat droppings. Classically, histoplasmosis has been categorized to the acute pulmonary, chronic granulomatous, and disseminated form. In the US, skin lesions are present in about 10-25 % of disseminated form.

Cutaneous manifestation of disseminated histoplasmosis is polymorphous. Multiple nonspecific papules, nodules with or without central erosions, molluscum-like lesions, acneiform eruption, or keratotic eruptions have been reported. Systemic findings including fever, chills, and weight loss are common in addition to varying degrees of respiratory and reticuloendothelial system involvement.

Diagnosis is based on histopathological identification of the 2-4 micrometer yeast with narrow based budding. In addition to the conventional H&E stain, GMS and PAS highlights the yeast. Culture remains the gold standard of histoplasmosis diagnosis and further characterization. However, given the 3-6 weeks incubation time, histoplasma urine antigen detection is used for more rapid diagnosis.

Treatment of disseminated histoplasmosis is based on the severity of the disease, with severe being associated with immunosuppression, septic signs, respiratory compromise, or pancytopenia. In patients with severe disseminated histoplasmosis, amphotericin B is used as first line therapy despite its nephrotoxicity. In cases of renal impairment, studies have shown itraconazole to be effective as well. Patients with mild clinical course can be treated with itraconazole initially. Antiretroviral therapy should be initiated in HIV affected patients. Patients who do not achieve immune recovery may require lifelong suppression with itraconazole.

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Key locations: thighs, lower back **CASE 10**

Presented by Divya Sachdev MD, and Warren Piette MD

History of Present Illness
A 69-year-old lady with a one-and-a-half-month history of painful skin lesions of her thighs and lower back was admitted for a non-ST-elevation myocardial infarction (NSTEMI). She had been hospitalized for multiple NSTEMIs and had undergone a left heart catheterization two months prior to presentation. During this time, she also developed new pain on her right foot and toes which was attributed to chronic ischemia.

Past Medical History
Hypertension, coronary artery disease s/p coronary arterial bypass graft (CABG), peripheral arterial disease, chronic kidney disease

Medications
Aspirin, atorvastatin, carvedilol, nifedipine, clopidogrel

Social History
Former smoker

Review of Systems
Positive for chest pain

Physical Exam
Upper lateral thighs with indurated, branching, necrotic, exquisitely tender plaques with erythematous borders and livedo reticularis. Lower back with smaller necrotic plaques.

Laboratory Data

	At presentation	One month prior	Reference range
BUN	25	27	8-20 mg/dL
Cr	1.5	1.8	0.6-1.4 mg/dL
Ca	9.7	9.9	8.5-10.5 mg/dL
Albumin	3.9	3.7	3.8-5.2 g/dL
WBC	13.8	8.7	4.4-10.6 k/uL
• Neut	• 9.3 (68%)	• 4.8 (55%)	• 2.2-6.9 k/uL
• Lymphs	• 3.2 (23%)	• 2.4 (28%)	• 1.2-3.4 k/uL
• Eos	• 0.1 (0.9%)	• 0.6 (7%)	• 0.0-0.4 k/uL
Hgb	10.4	12.0	11.7-14.9 g/dL
Plt	297	231	161-369 k/uL
Troponin	16.0	7.97	0.000-0.039 ng/mL

Histopathology
Punch biopsy, right upper lateral thigh: Inflamed vessels in the deep vascular plexus with needle shaped clefts; Von Kossa stain negative.

Diagnosis
Cutaneous cholesterol embolization syndrome

Treatment and Course
The patient was transferred to an outside hospital for further cardiac management.

Discussion

The diagnosis of cutaneous cholesterol embolization can be clinically challenging. It occurs more commonly in elderly men; however, the exact incidence is unknown due to inconsistencies in diagnosis and varying clinical presentation. Risk factors include hypertension, hypercholesterolemia, diabetes mellitus, peripheral vascular disease, advanced age and heavy smoking.

Cholesterol embolization may occur spontaneously or iatrogenically as a result of plaque rupture and release of cholesterol crystals. Plaque disruption can be caused by invasive angiography, major vessel surgery, angioplasty or thrombolytic therapy. It can also develop after four to eight weeks of anticoagulation therapy due to dissolution of the protective thrombi and fibrin surrounding an atheromatous plaque. Cholesterol emboli enter circulation and become lodged in small arterioles resulting in occlusion and an inflammatory reaction.

Clinical manifestations depend on the final anatomic location of the cholesterol emboli. The skin, gastrointestinal system, and kidneys are most commonly involved, although any organ system may be affected. Cutaneous manifestations are varied and include livedo reticularis, acral cyanosis, ulcers, nodules and purpura. Because the aorta and iliac arteries are the most common source of cholesterol crystals, lesions are typically found on the distal lower extremities. Although atypical, proximal involvement has been described with cutaneous presentations like the one presented in this case. These patients had necrotic lesions of the lower back, hips, buttocks, and lower abdomen.

Patients may also have associated constitutional symptoms such as fever and malaise. Possible lab findings include peripheral eosinophilia, elevated C-reactive protein or erythrocyte sedimentation rate, and evidence of end organ damage. Histopathology shows elongated clefts within the lumen of small subcutaneous vessels that may be surrounded by thrombus, hyperplastic intimal tissue, and giant cells.

Cholesterol embolization carries a poor prognosis with high morbidity and mortality. There is no definitive management guidelines and treatment is generally supportive. Potential therapies include high dose statins, systemic corticosteroids, antiplatelet agents, and pentoxifylline.

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Key location(s): face, upper extremities **CASE 11a**

Presented by Hana Stelle MD, and Warren Piette MD

History of Present Illness
A 42-year-old Hispanic female with a history of autoimmune hepatitis and end stage renal disease (ESRD) on hemodialysis presented with pruritic, burning skin lesions on her face, right arm, and right hand. The lesions initially appeared after missing a hemodialysis session and a recent trip to a lake. She had been diagnosed with SLE and SCLE several years prior, which was recalcitrant requiring multimodal treatment with both topical steroids and immunosuppressants including prednisone, azathioprine, and hydroxychloroquine.

Past Medical History
Systemic lupus erythematosus, subacute cutaneous lupus erythematosus, autoimmune hepatitis, ESRD on hemodialysis, hypertension

Medications
Prednisone, azathioprine, hydroxychloroquine, lovastatin, nifedipine, aspirin, ergocalciferol, triamcinolone

Social History
No history of tobacco or substance abuse

Review of Systems
Positive for fatigue, burning pain, pruritus
Negative for fevers, chills, weight loss, joint pain, abdominal pain

Physical Exam
Face: scattered erosions and 3-4 intact flaccid bullae; bilateral temples and cheeks with macular and reticulated hyperpigmentation
Right arm: 2 erosions
Right dorsal hand: pink, ill-defined arcuate dermal plaque

Laboratory Data
The following labs were remarkable/abnormal:
Note: Urinary porphyrins were not measured because the patient was anuric.

Hemoglobin	11.6 g/dL	[11.7-14.9 g/dL]
Ferritin	600 ng/mL	[11-307 ng/mL]
Creatinine	5.8 mg/dL	[0.6-1.4 mg/dL]
BUN	38 mg/dL	[8-20 mg/dL]
Serum Uroporphyrin	17.6 mcg/L	[≤ 0.2 mcg/L]
Heptacarboxyporphyrin	4.1 mcg/L	[≤ 0.2 mcg/L]
Hexacarboxyporphyrin	0.7 mcg/L	[≤ 0.3 mcg/L]
Pentacarboxyporphyrin	0.5 mcg/L	[≤ 0.4 mcg/L]
Coproporphyrin	2.7 mcg/L	[≤ 0.8 mcg/L]
Total Porphyrins	27.6 mcg/L	[1.0-5.6 mcg/L]

Diagnosis
Porphyria cutanea tarda

Treatment and Course

Because of her ESRD, the patient was treated with erythropoietin and serial, low-volume phlebotomy (on average 250cc twice per week with replacement with equivalent normal saline). HCQ 200mg daily that had been started many years prior for SLE was continued. Although her porphyrin profile has not yet improved, the vesiculobullous lesions healed with hypo- and hyperpigmentation, and she has not had a relapse since her initial presentation in September 2018.

Key location(s): face, upper extremities **CASE 11b**

Presented by Hana Stelle MD, and Warren Piette MD

History of Present Illness
A 50-year-old woman with ESRD on hemodialysis was admitted for right upper extremity swelling secondary to partial blockage of subclavian and brachiocephalic arteries and a one-month history of blisters on her hands. She also noted darkening of the skin on her face.

Past Medical History
Diabetes mellitus, ESRD on hemodialysis

Medications
Ropinirole, sevelamer, cinacalcet, amitriptyline, gabapentin, midodrine, glyburide, ibuprofen and aspirin

Social History
No history of tobacco or substance abuse

Review of Systems
Positive for pain, tenderness, swelling
Negative for fevers, chills, weight loss, joint pain, abdominal pain, nausea, vomiting

Physical Exam
Right dorsal hand: tense, fluid-filled blister on a non-erythematous base
Bilateral dorsal hands: multiple scattered erosions with hemorrhagic crust
Face: diffuse hyperpigmentation, hypertrichosis at the angle of the mandible

Laboratory Data
The following labs were remarkable/abnormal:
Note: Urinary porphyrins were not measured because the patient was anuric.

Hemoglobin	12g/dL	[11.7-14.9g/dL]
Creatinine	6.7mg/dL	[0.6-1.4mg/dL]
BUN	40mg/dL	[8-20mg/dL]
Serum Uroporphyrin	>1500 mcg/L	[≤ 0.2mcg/L]
Heptacarboxyporphyrin	651.9 mcg/L	[≤ 0.2mcg/L]
Hexacarboxyporphyrin	106.9 mcg/L	[≤ 0.3mcg/L]
Pentacarboxyporphyrin	12 mcg/L	[≤ 0.4mcg/L]
Coproporphyrin	1.6 mcg/L	[≤ 0.8mcg/L]
Total Porphyrins	>1500 mcg/L	[1.0-5.6mcg/L]

Diagnosis
Porphyria cutanea tarda

Treatment and Course
The patient was discharged from the hospital, and we await her return.

Discussion
While porphyria cutanea tarda (PCT) is the most common type of porphyria, it is estimated to affect only 0.0005% to 0.001% of the general population compared to 1.2% to 18% of patients receiving maintenance hemodialysis. In 75-95% there is no identifiable genetic predisposition

(type I), with the remaining 10-25% associated with an autosomal dominant defect (type II) in uroporphyrinogen decarboxylase (UROD). In virtually all cases, external factors are necessary for clinically apparent disease as the disease phenotype requires hepatic UROD deficiency to fall below 20% of normal. Both types result in abnormalities in the porphyrin-heme biosynthetic pathway with accumulation of highly carboxylated uroporphyrins in the plasma and skin. These molecules become excited by exposure to specific wavelengths of light, most notably the Soret band (400-410 nm) with the subsequent release of reactive oxygen species, leading to skin damage and blister formation.

Inciting factors include alcohol (>90% of cases), Hepatitis C virus (60-90%), neoplasms (e.g. hepatocellular carcinoma), hemochromatosis (17-47%), iron overload, hemodialysis in patients with end stage renal disease (ESRD), HIV, estrogens, and polychlorinated hydrocarbons. Although the precise pathophysiologic mechanism of PCT in hemodialyzed patients is unknown, several theories have been proposed: (1) decreased activity of UROD secondary to azotemia, (2) impaired ability to excrete porphyrins and poor elimination by dialysis, (3) interference of heme synthesis secondary to aluminum intoxication (less common today with aluminum-free dialysis water), (4) a state of iron overload resulting from a combination of frequent red blood cell transfusions, anemia of chronic disease, and chronic viral hepatitis infections leading to increased oxidative stress and subsequent formation of inhibitors of UROD.

Dermatologic manifestations of PCT include photosensitivity, increased skin fragility, subepidermal bullae, erosions, milia, hyperpigmentation, hypertrichosis, and scarring in photodistributed areas especially face, dorsal hands, and forearms. Serum and fecal porphyrins can confirm the diagnosis and histopathology and direct immunofluorescence are supportive. In patients who do not have end stage renal disease, urine porphyrins are also diagnostic. Histologic findings typically include cell-poor subepidermal bullae with festooning of dermal papillae, thickening of the basement membrane, and immunoglobulins (IgG>IgM), complement, and fibrinogen at the dermal epidermal junction and around dermal blood vessels on immunofluorescence. Urine or plasma porphyrin profiles show a predominance of uroporphyrin and heptacarboxyporphyrin in addition to elevated fecal heptacarboxyl porphyrin and isocoproporphyrin. As in our patients, many ESRD patients are unable to undergo analysis of urine porphyrins as they are anuric. This condition should be differentiated from pseudoporphyria which resembles PCT clinically and histologically but usually without an abnormal porphyrin profile. While an abnormal porphyrin profile is almost always diagnostic of PCT in patients without renal failure, serum porphyrins have been found to be moderately elevated in patients with end stage renal disease without cutaneous manifestations of disease. The additional findings of hypertrichosis, hyperpigmentation, sclerodermoid changes, and dystrophic calcification strongly suggest PCT. An additional factor in patient A is the known photosensitivity of patients with SCLE. The question of whether this lowers the threshold for manifestations of porphyrin related blistering is unanswered.

Standard therapy (non-ESRD) consists of repeated phlebotomy (~500mL every two weeks as tolerated) and/or low-dose antimalarials (e.g. 200 mg of hydroxychloroquine or 125 mg of chloroquine twice weekly). Administration of higher doses of these antimalarials can lead to hepatotoxicity. Treatment of PCT in ESRD patients presents a unique challenge as hydroxychloroquine is often ineffective, serial phlebotomies are poorly tolerated in already anemia-prone patients, and iron-chelating agents are less efficient in removing iron and contribute to worsening anemia. As in all patients with PCT, removal of contributory factors, especially alcohol, strict photoprotective measures, and monitoring of serum porphyrins should be employed. There has been variable success with erythropoietin alone and in combination with small-volume (50-100cc) phlebotomy, renal transplantation, plasma exchange, and deferoxamine in combination with ferric carboxymaltose.

Fortunately, with the progress in the care of ESRD patients including erythropoietin and the use of high-flux membranes, PCT is no longer a frequent complication of ESRD. Nonetheless, it is important to recognize this clinical entity and understand the limitations of current treatment modalities in this particular subset of patients.

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