Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, May 9, 2018
Gleacher Center – Chicago, IL

Conference Host:
Department of Dermatology
Rush University Medical Center
Chicago, Illinois

Program

Host: Rush University
Wednesday, May 9, 2018
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** "Primer on Molecular Profiling and Next Generation Sequencing" *Hensin Tsao, 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** MALKINSON LECTURE - "Update on Melanoma Therapeutics" *Hensin Tsao, MD, PhD*
2:00 p.m.	**Meeting adjourns**

Mark the Date!

Next meeting will be the CDS/IDS Joint Conference & Awards Luncheon
Wednesday, June 6th; Stephens Convention Center, Rosemont

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

Guest Speaker

HENSIN TSAO, MD, PHD
Harvard Medical School &
Massachusetts General Hospital
Boston, MA

Hensin Tsao, MD, PhD is a board-certified dermatologist and Professor of Dermatology at Harvard Medical School. Presently, he is Director of the Melanoma and Pigmented Lesion Center, the Melanoma Genetics Program, and the Skin Cancer Genetics Laboratory in the Wellman Center for Photomedicine, all of which are at the Massachusetts General Hospital. Beyond patient care, he dedicates much of his time to melanoma research and the education of medical students, dermatology residents, and fellows.

Dr. Tsao received his undergraduate degree from Brown University where he graduated magna cum laude and Phi Beta Kappa. Later, he graduated Alpha Omega Alpha from the Columbia University College of Physicians and Surgeons with an MD degree and received his PhD from Columbia University Graduate School of Arts of Sciences. Dr. Tsao completed one year of clinical training in internal medicine and three years of dermatology residency, as well as a one-year Melanoma Fellowship in the Harvard-affliated hospitals. He concluded his training with a postdoctoral fellowship in the Division of Oncology at Massachusetts General Hospital.

Dr. Tsao supervises an active cancer genetics laboratory and is the author of more than 100 scholarly articles, reviews, abstracts, textbook chapters, and online media texts. He has also delivered more than 100 lectures on melanoma, genetics, and skin disease throughout the world.

CME Information

May 9, 2018

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 1903 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 2017/18 series of meetings, the participant should be able to:

1. Discuss key factors in the diagnosis and treatment for allergic conditions, viral diseases and bacterial infections.
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 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 4.5 *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, Hensin Tsao, MD PhD, nor any of the planning committee members have any conflicts of interest to disclose.

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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.

Rush University
Department of Dermatology

Resident Case Presentations

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 1**

Presented by Meredith Morse, MD and Arthur Rhodes, MD, MPH
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 16 year-old white woman presented for melanoma and skin cancer screening. She was referred by another dermatologist for a grouping of numerous Spitz tumors on her left lateral upper thigh. She had no personal history of melanoma or other non-melanocytic skin cancers. Her father has had melanoma. The first lesion on her left lateral upper thigh was noted 4 years prior to presentation. Pathology revealed a "Spitz tumor." Since that time, she has had 11 separate lesions biopsied, all from the same area of her left lateral upper thigh. All subsequent pathology specimens from this lesion were interpreted as "Spitz tumors." The tumors with positive margins were re-excised. New lesions were appearing approximately every 6 months. Her most recent biopsy had been 1.5 years before presenting to us.

PAST MEDICAL HISTORY

No significant medical history

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

Father – melanoma
Mother's mother – lung cancer

SOCIAL HISTORY

No tobacco use

PHYSICAL EXAM

Examination revealed a healthy-appearing young woman whose total mucocutaneous examination was unremarkable except for the lesions of concern. There were 11 red papules and plaques in an area measuring 7 cm x 6 cm on the left lateral upper thigh. All lesions were red, firm, and non-blanching, ranging in size from 3 mm to 8 mm in diameter. Well-healed scars were present in this area. Dermoscopy of several lesions all revealed the same pattern: haphazardly distributed white streaks scattered among a confluence of red dots.

LABORATORY RESULTS

None

DIAGNOSIS

Agminated epithelioid cell Spitz tumors

TREATMENT AND COURSE

The patient was sent for surgical excision of all visible lesions. It was recommended that she be seen for a total mucocutaneous examination for melanoma surveillance every 6 months.

DISCUSSION

Epithelioid cell and/or spindle cell Spitz tumors are said to be benign, acquired melanocytic neoplasms. Lesions are typically solitary and most often appear in childhood, adolescence, or early adulthood. Agminated (meaning “clustered or grouped”) Spitz tumors are exceedingly rare. To date fewer than 50 cases of agminated Spitz tumors have been reported. Agminated Spitz tumors have the same morphologic and histologic appearance as solitary Spitz tumors.

Agminated Spitz tumors have been reported to occur on healthy-appearing skin, hyperpigmented skin (multiple lesions in pigmented macules), or hypopigmented skin. Agminated Spitz tumors developing within a nevus spilus has also been reported. Spitz tumors presenting in agminated lesions have been reported to number from 2 to several hundred. The most frequent site for agminated Spitz tumors is the face followed by the upper extremities. In published case reports, 50% of cases occurred in patients younger than 5 years of age, with no gender predilection.

The etiology of agminated Spitz tumors is unknown. Previous sunburns, trauma from excision of isolated lesions, and radiation therapy have been proposed. None of these potential inciting events were pertinent in our patient. An epithelioid cell Spitz tumor can sometimes be clinically and histologically difficult to distinguish from amelanotic melanoma. Current guidelines recommend complete excision of isolated Spitz tumors. Such a recommendation may be a challenge in patients who have numerous agminated lesions.

Spitz tumors most often appear as a single lesion. Their relation to melanoma risk is notable. In one large, retrospective, single-institution case series, there was a reported increased melanoma risk for patients who had a diagnosis of a Spitz tumor. Among 144 Spitz tumor patients followed for 30 years, there were 6 documented invasive melanomas. This was an 8-fold increased risk compared to the general population matched for age and sex. One may conclude from this study that having a Spitz tumor is a significant risk factor for development of melanoma.

The long-term clinical outcome of patients who have Spitz tumors in general has been controversial. Spitz tumors do have the propensity for local regional lymph node metastasis, but with low distant metastatic potential. Microscopic disease in sentinel lymph node biopsy (SLNB) occurs in approximately 40% of patients. Widespread metastatic disease related to a Spitz tumor likely suggests a misdiagnosis of the original lesion. The utility of SLNB for patients who have one or more Spitz tumors is controversial.

The agminated Spitz tumors in published cases were treated with surgical excision, using skin grafting when necessary. Any new lesion that arises within the site of agminated Spitz tumors should be regarded with clinical suspicion and considered for excision. Patients who have agminated Spitz tumors should be considered for lifetime surveillance, with excisional biopsy of new lesions. High-resolution digital imaging is invaluable for patients who have agminated Spitz tumors. Our patient was sent for surgical excision of all visible tumors, with the recommendation of lifetime follow-up at 4 to 6 month intervals.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 2**

Presented by Stacie Clark, MD, Mark D. Hoffman, MD and Sarah Everakes, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 66 year old woman presented to dermatology clinic for routine follow up of lymphomatoid papulosis type B, (LyP), diagnosed by skin biopsy 2 years prior. Her cutaneous symptoms had been well controlled with topical corticosteroids as needed. Prior systemic workup following her diagnosis of lymphomatoid papulosis, including flow cytometry, SPEP, and CT of the chest, abdomen and pelvis was within normal limits.

During the office visit, the patient incidentally mentioned a 3-month history of swelling, pain and erythema of the bilateral lower extremities. She had also noticed intermittent forearm pain and swelling, with a possible change in the texture of her skin, dyspnea on exertion, and generalized muscle weakness.

PAST MEDICAL HISTORY

LyP – Type B
Osteoporosis
Diverticulosis

MEDICATIONS

Amitriptyline
Ativan
Alendronate
Lansoprazole
Topical corticosteroid (unknown type)

FAMILY HISTORY

Father – Bladder and prostate cancer

SOCIAL HISTORY

No tobacco or illicit drug use. Rare alcohol consumption.

PHYSICAL EXAM

Subtle rippling change was noted in the upper extremities, without obvious evidence of induration, erythema or edema during initial examination. No lesions suggestive of lymphomatoid papulosis were noted.

Repeat examination 1 month later revealed pseudocellulite changes of the arms, legs and hips. A positive “groove sign” was noted on the bilateral upper extremities.

HISTOPATHOLOGY

Biopsy of the skin and subcutaneous tissue overlying the right gastrocnemius muscle demonstrated marked dermal sclerosis, perivascular and periadnexal lymphocytic infiltrate and focal thickening of the fibrous septa of the fat. There was marked thickening of the underlying fascia and infiltration by mononuclear inflammatory cells with scattered eosinophils. Skeletal muscle fibers showed myofiber degeneration and lymphocytic infiltration.

Prior LyP biopsy (2016):
Biopsy of the skin demonstrates a superficial and deep perivascular and patchy lichenoid infiltrate of lymphoid cells with scattered larger atypical forms. Many of the lymphocytes extend to the overlying epidermis. The lymphoid infiltrate is composed mostly of CD3 positive T cells with a few scattered CD20 positive B cells. A majority of the T cells are CD4 positive with a CD4 to CD8 ratio of approximately 5:1. Stain for CD30 highlights a generous population of large lymphoid cells.

LABORATORY RESULTS
ANA, ANCA, Anti-RNP, Anti-Smith, SSA/SSB, C3/C4 and hypercoagulability workup were all within normal limits.

LABORATORY TEST	RESULT	REFERENCE RANGE
Anti-dsDNA	**45 IU/L**	0-26 IU/L
C reactive protein	**14.9 mg/L**	0-8 mg/L
White blood cell	**7.81 K/uL**	4.00-10.00 K/uL
Eosinophil #	**1.55 K/uL**	0-0.6 K/uL
Eosinophil %	**19.8%**	0-6%
Hemoglobin	12 g/dL	12.0-16.0 g/dL
Hematocrit	35.8%	37-47%
Platelets	301 K/uL	150-399 K/uL

Prior LyP workup:

Flow cytometry (2016): No immunophenotypic evidence of lymphoma.

SPEP/SIEP (2016): No paraprotein detected. No monoclonal proteins detected. Serum free light chain normal pattern, no monoclonal free light chains.

RADIOLOGY
Magnetic resonance imaging of the left lower extremity demonstrated circumferential thickening of the superficial fascia with corresponding enhancement. There was minimal thickening of the deep fascia with corresponding enhancement. Minimal edema in the soleus muscle was noted.

Computed tomography of the chest, abdomen and pelvis in 2016 was within normal limits.

DIAGNOSIS
Eosinophilic fasciitis in the setting of lymphomatoid papulosis (type B)

TREATMENT AND COURSE
The patient was started on prednisone 40 mg daily. After 1 month of treatment, she noted greater than 75% improvement in both peripheral edema and dyspnea on exertion. After 2 months, peripheral eosinophilia had resolved. She was transitioned to methotrexate and her dose was titrated to 20 mg weekly. At this dose, the patient noted increased shortness of breath, cough, and fatigue. Infectious disease workup was negative and no eosinophils were noted in bronchial washings. CT of the chest demonstrated ground glass opacities and consolidation. Due to concerns for methotrexate pneumonitis, the patient was switched to mycophenolate mofetil 500 mg BID and continued on prednisone 30 mg daily. Repeat CT and pulmonary function tests normalized and symptoms of chest constriction resolved. She is currently well controlled on mycophenolate mofetil 1000 mg BID and prednisone 15 mg daily.

DISCUSSION

Eosinophilic fasciitis (EF), first described by Shulman in 1975, is a fibrosing disorder characterized by induration of the extremities associated with peripheral eosinophilia, hypergammaglobluinemia, and elevated erythrocyte sedimentation rate. Although the exact etiology of EF remains unclear, multiple hypotheses regarding causality have been proposed. In approximately 30-46% of patients with EF, a history of strenuous physical activity precedes the clinical findings, suggesting a role of muscle trauma in the etiology of the disorder. Exposure to specific drugs and chemical compounds has also been suggested as a possible triggering event in EF. These include influenza vaccination, statins, ramipril, phenytoin, or subcutaneous heparin. Of note, exposure to L-tryptophan has been linked to eosinophilia-myalgia syndrome, a similar eosinophilic dermatosis, characterized by severe myalgias, fever, dyspnea, edema, peripheral eosinophilia and a macular exanthem preceding a chronic, sclerodermoid induration of the extremities. Rare reports suggest infections (such as *Borrelia*), autoimmune disease or graft-versus-host disease as other possible triggering factors for EF.

The pathogenesis of EF is unknown, however a humoral immune mechanism is believed to play a role. Hypergammaglobulinemia occurs in 35-100% of patients with EF and deposition of IgG, IgM and C3 in the fascia has been reported. It has been hypothesized that immune complex deposition in the fascia attracts eosinophils capable of stimulating fibroblast proliferation, resulting in the characteristic sclerosis of EF.

EF affects males and females equally, with a predominance in middle-aged adults. Initial manifestations include abrupt onset of symmetric edema, pain and stiffness of the upper or lower extremities. The hands, feet and face are usually spared. Edema is progressively replaced by induration of skin with characteristic "pseudo-cellulite" appearance or a "groove sign" along the course of a vein. Fascial fibrosis can ultimately lead to joint contracture and tendon retraction. Extracutaneous manifestations are rare, but include symmetric polyarthritis, tenosynovitis, esophageal dysmotility, pulmonary fibrosis, and pericarditis. Absence of sclerodactyly, Raynaud's phenomenon and abnormal nailfold capillaries help to differentiate EF from systemic sclerosis. Laboratory findings include elevated ESR, hypergammaglobulinemia and peripheral eosinophilia. Antinuclear antibodies and complement levels are generally normal. Hematologic abnormalities such as myelomonocytic leukemia, Hodgkin's disease, mycosis fungoides, chronic lymphocytic leukemia and myeloproliferative disorders have been reported in approximately 10% of patients with EF.

Diagnosis is best established by full-thickness biopsy and magnetic resonance imaging (MRI). The characteristic MRI finding of EF is enhanced signal intensity in the fascia, representing edema. This finding is directly proportional to disease activity and can be used to evaluate response to treatment. Histopathology demonstrates thickening of the deep fascia, up to 10-50 times the normal width. A patchy infiltrate of lymphocytes and plasma cells with occasional eosinophils and mast cells is seen. Fibrosis of the dermis may be demonstrated.

Systemic corticosteroids, at a dose of 0.5-1 mg/kg/day, are considered first-line therapy for EF. Partial to complete response is achieved in 70-90% of patients treated with corticosteroids. In steroid-resistant patients, alternative therapies such as methotrexate, cyclosporine, dapsone, infliximab, PUVA or ECP have been used with variable success. The use of mycophenolate mofetil in the treatment of EF has also been reported. It is suspected that in addition to its inhibitory effects on the proliferative response of T and B lymphocytes, mycophenolate mofetil also has intrinsic antifibrotic properties. Theoretically, classic immunosuppressive medications increase the risk of lymphomatous malignancies and are relatively contraindicated in patients

with an underlying predisposition to such malignancies, as is the case in lymphomatoid papulosis. However, unlike other immunosuppressive agents, mycophenolate mofetil does not produce an abnormal nucleotide analogue and is renally cleared without DNA integration. Therefore, compared to other immunosuppressive medications, mycophenolate mofetil may have a decreased risk of mutagenicity and has been used safely and successfully in patients with lymphomatoid papulosis.

As previously noted, EF has been associated with a variety of hematologic disorders, both benign and malignant. In a subset of patients with EF, the presence of circulating clonal T-cell populations has been identified. Such abnormal T-cell clones ($CD3^+CD4^-CD8^-$ or $CD3^-CD4^+$) have been similarly described in patients with lymphocytic hypereosinophilic syndrome (HES). Although it is unknown whether these clones are a consequence of chronic inflammation or whether they represent a pre-lymphomatous condition, it is suspected that they play a role in the pathogenesis of hypereosinophilia through the hyperproduction of interleukin-5 (IL-5), a regulator of eosinophil development and function. The release of IL-5 by activated, abnormal clonal lymphocytes likely leads to the development of peripheral eosinophilia and consequent clinical manifestations in both HES and EF. In such patients, the possibility of coexisting or future occurrence of hematologic malignancy must be considered.

LyP is a CD30+ lymphoproliferative disorder characterized by chronic, recurrent papulonecrotic or papulonodular lesions. Red-brown papules and nodules occur as single or multiple crops, predominately affecting the trunk and limbs, with a tendency to regress spontaneously over 3-8 weeks. Six subtypes (A-E), based on histopathologic findings, have been described, however the subtypes do not differ clinically. In up to 20% of patients, LyP may be associated with other cutaneous or systemic lymphomas, with mycosis fungoides and anaplastic large cell lymphoma being the most common. Sixty - 70% of LyP patients have clonally rearranged TCR genes and identical T-cell clones have been demonstrated in LyP patients who subsequently develop mycosis fungoides or other associated lymphoma lesions. As such, there is continued discussion as to whether LyP is a malignant, premalignant or benign condition.

To date, there are no published reports of EF arising in the setting of LyP, however there are multiple reports of LyP in association with HES. In such cases, aberrant clonal CD30+ lymphocytes are thought to produce a Th2 cytokine profile, including IL-5, resulting in peripheral hypereosinophilia and subsequent HES. It is plausible, that a similar abnormal CD30+ induced eosinopoietic cytokine milieu in an LyP patient could ultimately manifest clinically as EF.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 3**

Presented by Andrew Thompson, MD and Claudia Hernandez, MD
Department of Dermatology, RUSH University Medical Center

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE 4**

Presented by Nick Blickenstaff, MD and Mark D Hoffman, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

This patient is a 24 year-old woman who was referred to RUSH Dermatology in June 2017 for evaluation of groin ulcerations. She was initially diagnosed with systemic lupus erythematous (SLE) in the summer of 2015 and was receiving care by a rheumatologist in Texas. She was started on hydroxychloroquine but continued to have fevers and pleurisy so mycophenolate mofetil was added. Mycophenolate mofetil could not be titrated to more than 1000 mg twice daily due to dose-limiting alopecia. In March 2016 rituximab was initiated due to persistently low complement levels, cytopenia and synovitis. Mycophenolate mofetil and hydroxychloroquine were also continued. She started to develop perineal “abscesses” two months following the onset of the first rituximab infusion. These lesions were felt to represent necrotizing fasciitis in the perineal and buttock area. She also had two fistulas, one of which was communicating with the anus. In a period of 3 months she underwent multiple I&Ds, serial debridement, and muscle flap placement; however, the condition seemed to be getting worse. The wound seemed to be getting larger and was accompanied by worsening pain. A diverting colostomy was done preventatively to help heal the areas. Eventually, she underwent multiple reconstructive procedures of the perineum (L gracilis flap, gluteal flap, skin graft). Mycophenolate mofetil was stopped in August 2016 by the infectious disease service to facilitate healing. A second rituximab infusion was given in October 2016 in Texas which was associated with further exacerbation of her wounds.

PAST MEDICAL HISTORY

Antiphospholipid antibody positive
Systemic lupus erythematosus
Sjogren's disease
Raynaud’s disease
No history of prior DVT or known IBD

MEDICATIONS

Hydroxychloroquine
Prednisone
s/p Rituximab infusions (x2)

ALLERGIES

Sulfa (sulfonamide antibiotics) - unknown reaction

FAMILY HISTORY

Sister - psoriasis with psoriatic arthritis

SOCIAL HISTORY

No tobacco or recreational drug use.

PHYSICAL EXAM

Pronounced edema of the labia majora with a solitary 3.5 x 1.5 cm well demarcated, clean ulceration on the left labium majus. It was tender and non-indurated. The left medial thigh had

scarring from prior instrumentation/grafting. There was no involvement of the oral mucosa or eyes.

HISTOPATHOLOGY

Biopsy of the posterior vaginal wall on 5/2017 showed ulcerated mucosa with granulation tissue formation and marked acute and chronic inflammation. Biopsy of the left labium demonstrated ulcerated squamous mucosa with underlying acute and chronic inflammation, granulation tissue, and fibrosis.

Biopsies of the right and left labium majus in 6/2017 showed ulcerated squamous mucosa with granulation tissue, marked acute and chronic inflammation, and few gram positive organisms. GMS and Gram stains with appropriate controls revealed gram positive cocci in clusters, GMS was non-contributory.

LABORATORY RESULTS

Outside Hospital (2015) – ANA+ (titer 1:2560), anti-dsDNA+, SSA/SSB+, RF+, anticardiolipin antibody+, beta-2-glycoprotein antibody+; complement panel, RNP, anti-Sm were all within normal limits; bacteriology, viral swabs, and serology excluded HIV, syphilis, HSV, and other infections

LABORATORY TEST	RESULT	REFERENCE RANGE
White Blood Cell	17.35 K/uL	4.00-10.00 K/uL
Alanine aminotransferase (ALT)	89 U/L	0-40 U/L

Remaining CBC, CMP, and urinalysis values were all within normal limits.

DIAGNOSTIC TESTING

Colonoscopy with colonoscopic biopsies of the terminal ileum, right colon, left colon and rectum demonstrated no diagnostic abnormalities

DIAGNOSIS

Vulvovaginal pyoderma gangrenosum in association with rituximab

TREATMENT AND COURSE

Upon returning from Chicago the patient was initially evaluated by dermatology at University of Chicago and diagnosed with pyoderma gangrenosum. She was started on prednisone 30 mg daily, cyclosporine 3 mg/kg (titrated to 5 mg/kg) and tacrolimus 0.1% ointment twice daily. She presented to RUSH rheumatology for continued SLE management, and was subsequently referred to dermatology who continued the patient on cyclosporine and increased her prednisone. Silvadene cream was added for treatment of her wounds. She was eventually able to discontinue prednisone, and taper cyclosporine following healing of the ulcers with no additional flares. She remained on hydroxychloroquine.

At the most recent follow up visit, the patient reported complete healing of prior ulcerations. There was no inflammation, tenderness, or swelling seen on examination. Her cyclosporine is being tapered and was reduced to 2 mg/kg.

DISCUSSION

Pyoderma gangrenosum (PG) is an uncommon inflammatory and ulcerative skin disease with four major clinical forms: ulcerative, bullous, pustular, and vegetative. Cutaneous lesions are painful and most frequently occur on the lower extremities, especially the pretibial area, but they

can occur anywhere, including on mucus membranes and peristomal sites. The incidence is estimated to be 3-10 cases per 1 million people per year. The pathophysiology of PG is speculative but proposed mechanisms include loss of innate immune regulation and/or altered neutrophil chemotaxis. Biopsies most characteristically demonstrate neutrophilia, and the concept of neutrophil dysregulation has also been supported by the clinical response that may be seen with the use of anti-neutrophilic agents including colchicine and dapsone.

PG has distinctive clinical features, but its presentation can generate an extensive differential. Infections, alternative inflammatory conditions including cutaneous Crohn's disease, malignancy, vascular disease, drugs, exogenous or factitial injury, Behcet's disease, non-sexually acquired genital ulcers (NSAGU) and other neutrophilic dermatoses must be excluded before a diagnosis of pyoderma gangrenosum can confidently be made. Certain criteria have been proposed to aid in its diagnosis. These include meeting both suggested major criteria and at least two minor criteria, with major criteria being: 1) rapid progression of a painful, necrolytic cutaneous ulcer with an irregular, violaceous, and undermined border, and 2) other causes of cutaneous ulceration have been excluded. The minor criteria include: 1) history suggestive of pathergy or clinical findings of cribriform scarring, 2) systemic diseases associated with PG, 3) histopathologic findings (sterile dermal neutrophilia, +/- mixed inflammation, +/-lymphocytic vasculitis, and 4) treatment response (rapid response to systemic steroid treatment). Common systemic diseases associated with PG include inflammatory bowel disease, rheumatoid arthritis, and hematologic malignancies; PG may also occur in the context of autoimmune conditions.

Rituximab is a monoclonal antibody directed against the CD-20 antigen present on the surface of mature B cells. It was first approved for the treatment of low grade B cell non-Hodgkin lymphoma in 1997, and now carries indications for CLL, rheumatoid arthritis, Wegener's granulomatosis and microscopic polyangiitis. In addition to its therapeutic indications, rituximab may be efficacious in immunobullous dermatoses, SLE, cutaneous lupus erythematosus, chronic GVHD, and dermatomyositis.

According to a 2015 case series, there have been 9 cases of vulvar PG without rituximab and six cases of vulvar PG associated with rituximab published in the literature. All six of the patients who developed PG in association with rituximab were being treated for B cell non-Hodgkin lymphoma. Ages ranged from 50-74, with an average of 59 years. All patients had large, deep purulent vulvar ulcers, with five of patients also suffering extensive involvement of the vagina. They all reported severe pain, and four of the patients had associated heavy discharge. Two of the six patients were found to have vulvo-anal fistulas.

All previously documented cases of rituximab associated vulvar PG have been in patients with B-cell non-Hodgkin lymphoma. Our patient represents a unique case of genital PG associated with rituximab used for SLE management. Her presentation was similar to the cases discussed above, with the development of large painful vulvar ulcers and two fistulas following rituximab treatment. The ulcerations were exacerbated following a subsequent rituximab infusion. This was followed by a rapid healing response with immunosuppressive therapy using cyclosporine and prednisone. Other etiologies of her condition were excluded, making genital PG the likely diagnosis.

Clinicians should be aware of the association between rituximab and genital PG, particularly in severe, refractory non-infectious genital ulcerations. The proposed mechanism by which rituximab might contribute to development of PG is via complement activation and antibody binding of FCγ receptor sites resulting in direct activation of neutrophils and apoptosis. This

complication can greatly affect the psychosocial aspects of a patient's quality of life. Prior to treatment, our patient was experiencing such severe dysuria she needed to sit in warm water and use hydrocodone and acetaminophen in order to urinate. Her wedding planning was delayed and she required counseling for concerns about sexual function and the integrity of her genital area.

Once recognized, PG can be effectively treated. Therapy may include use of oral glucocorticoids, cyclosporine, mycophenolate mofetil, azathioprine, methotrexate, dapsone or infliximab. Other options include etanercept, adalimumab, ustekinumab, IVIG, granulocyte apheresis, and thalidomide. For small or slowly developing lesions, TCN-class antimicrobials or topical therapy with glucocorticoids, tacrolimus, can also be used, as well as injections of glucocorticoids.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 5**

Presented by Stacie Clark, MD and Claudia Hernandez, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 60 year old male presented to Dermatology for evaluation of a progressive, pruritic cutaneous eruption that started on bilateral dorsal hands and arms. His medical history was significant for metastatic adenocarcinoma of the lung for which he had been receiving infusions of nivolumab, a programmed death (PD)-1 receptor inhibitor, for the previous 5 months. The patient and his oncologist noted that the eruption worsened with each infusion of nivolumab and despite treatment with fluocinolone cream, had spread to his chest and back.

PAST MEDICAL HISTORY

Prostate cancer
Chronic renal disease
Pulmonary embolism s/p knee arthroplasty
Degenerative joint disease
Microvascular ischemic disease
Gastric ulcer

PAST SURGICAL HISTORY

Cholecystectomy
Laminectomy
Right total knee arthroplasty
Left total hip arthroplasty
Prostatectomy

MEDICATIONS

Enoxaparin
Gabapentin
Albuterol
Oxycodone

ALLERGIES

Iodine

FAMILY HISTORY

Mother – gastric cancer
Father – prostate cancer
Brother – colon cancer

SOCIAL HISTORY

Current smoker, forty pack year history

PHYSICAL EXAM

Clinical examination revealed innumerable skin colored to erythematous flat-topped papules on the upper extremities, chest, back and neck. The oral mucosa was clear.

HISTOPATHOLOGY

Histopathology revealed a multifocal lichenoid interface dermatitis with dyskeratosis. There were rare dermal eosinophils and pigment laden macrophages.

DIAGNOSIS

Lichenoid eruption secondary to programmed death (PD)-1 receptor inhibitor therapy

TREATMENT AND COURSE

Despite treatment with topical corticosteroids, the patient's cutaneous eruption continued to progress. Nivolumab was discontinued and the rash gradually improved. Treatment with next line therapy will begin upon clinical progression of the patient's adenocarcinoma.

DISCUSSION

Immune checkpoint targeted agents are an increasingly utilized method of immunotherapy in the treatment of cancer. These targeted therapies include ipilimumab, FDA approved for the treatment of unresectable or metastatic melanoma, and nivolumab and pembrolizumab, both approved for the treatment of unresectable or metastatic melanoma and non-small cell lung carcinoma, as well as other visceral and hematologic malignancies. The cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death receptor-1 (PD-1)/PD ligand-1 (PD-L1) signaling pathways are critical mediators of tumor-induced immune suppression. CTLA-4 is a co-inhibitory molecule present on the surface of activated circulating naïve and memory T cells, which, upon binding its ligands (CD80 and CD86), inhibits T cell proliferation. The PD-1 pathway appears to be primarily active against T cell activity in the peripheral tissues, inhibiting T-cell proliferation and subsequently the anti-tumor response. Pharmacological inhibition of either the CLTA-4 (ipilimumab) or PD-1 (nivolumab and pembrolizumab) pathways enhances T cell activation and promotes cytotoxic T cell activity against cancer cells.

The nonspecific enhanced immune response promoted by the immune checkpoint inhibitors leads to a variety of adverse effects, particularly in the skin. Cutaneous adverse effects associated with ipilimumab (CTLA-4 inhibition) range from pruritus and morbilliform eruption to toxic epidermal necrolysis. These reactions tend to occur early in the course of treatment, usually 3-6 weeks after initiation of the drug, and appear to be dose dependent. In contrast, cutaneous toxicities secondary to nivolumab and pembrolizumab (PD-1 receptor inhibition) tend to be less severe and have a slower onset of action, with reports ranging from 4-10 months after initiation of therapy. Approximately 49% of patients started on single agent anti-PD-1 therapy for melanoma developed cutaneous toxicity, with pruritus, lichenoid eruptions, eczematous eruptions, and vitiligo being the most common reactions, occurring alone or in combination. Alopecia, urticaria and autoimmune bullous reactions are less frequently reported. Although the safety profile of pembrolizumab and nivolumab are similar, it is hypothesized that pembrolizumab, a humanized monoclonal antibody, may have a slightly greater immunogenic potential than nivolumab, a fully human monoclonal antibody. Combination therapy of CTLA-4 and PD-1 receptor inhibitors results in more severe cutaneous adverse effects. General immunologic enhancement secondary to checkpoint inhibitors can also lead to a variety of systemic side effects, including colitis, hepatitis, pneumonitis and endocrinopathies.

In a recent study by Hwang et al, approximately 17% of patients on anti-PD-1 therapy developed a lichenoid reaction with mean time to onset approximately 8.3 months. Lesions most commonly appear on the trunk and extremities, frequently sparing the face. Oral involvement has been reported, commonly affecting the lips, tongue, gingivae and buccal mucosa. Histopathology typically demonstrates a dense band-like or interface lymphocytic infiltrate with

varying degrees of dyskeratosis, hyperkeratosis, and hypergranulosis. Occasional features such as parakeratosis, spongiosis and eosinophils support the diagnosis of a lichenoid drug eruption.

The severity of cutaneous drug reactions is graded according to the common toxic effects criteria. The majority of lichenoid eruptions secondary to PD-1 receptor inhibition represent grade I or II adverse events (pruritus with or without rash, <50% body surface area). These may be self-limited and generally respond well to topical corticosteroids. More severe dermatologic toxicities, including a symptomatic eruption involving greater than 50% of the body surface area (grade III adverse event) often require systemic corticosteroids with or without discontinuation of the inciting agent, as was the case for our patient.

The correlation between immune checkpoint inhibitor mediated cutaneous toxicity and treatment response remains unclear. However, early studies in patients who developed dermatologic adverse reactions during treatment with pembrolizumab or nivolumab demonstrated longer progression-free intervals and increased overall survival, respectively. This data is promising but remains to be validated by prospective analyses.

Immune checkpoint inhibition is an increasingly common therapy for the treatment of advanced carcinoma, with dermatologic toxicity being one of the most frequently reported adverse events. Recognition of these eruptions and knowledge regarding their treatment is critical for optimizing care for patients receiving these therapies.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 6**

Presented by Meredith Morse, MD and Warren Piette, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

The patient is a 39 year-old white female who presented to her gynecologist 2 years ago for vulvar pruritus and pain. She was treated with oral fluconazole and topical steroids without relief. This led to her gynecologist performing a skin biopsy which revealed a diagnosis of Langerhans cell histiocytosis (CD1a+, S100+, CD 207+). Systemic work-up including blood work, thyroid and hepatic testing, CT of the chest, abdomen and pelvis, bone scan, and bone marrow biopsy were negative. She was treated with radiation (3000cGy) to her pelvis with resolution of her symptoms.

She remained clear for 4 months, at which time she presented to RUSH with recurrence of her initial symptoms including vulvar pruritus, burning pain, and drainage. She also began developing small papules and erosions in her left axilla. Complete review of symptoms was negative. A repeat biopsy was performed over her mons pubis. Results confirmed a diagnosis of Langerhans cell histiocytosis (LCH). KOH, HSV-1, and HSV-2 PCR were all negative.

She was referred to hematology/oncology at RUSH's cancer center and started on vinblastine induction therapy [6 mg/sq meter (12 mg weekly x 6 weeks)] with prednisone 80 mg daily. After induction was completed, she noted less pain in her vulvar area as well as her left axilla and had a second induction 2 months later. She completed 6 treatments over the next 4 months with significant improvement.

Weekly vinblastine infusions were continued a total of 12 months of treatment with complete clearance of her skin disease and symptoms. Her last vinblastine infusion was 4 months ago, however, 1 month later she noted recurrent left axillary pain along with small open sores as well as perineal discomfort. The decision was made to administer radiation therapy to the left axilla. Two months after finishing vinblastine treatment, she had almost complete recurrence of disease along with discomfort and drainage in the affected areas.

PAST MEDICAL HISTORY

Hypertension
Diabetes mellitus (insulin-requiring while on long-term prednisone therapy for LCH treatment)

MEDICATIONS

Glimepiride
Metformin
Ferrous Fumarate and Magnesium (while on vinblastine)
Insulin (while on prednisone)

ALLERGIES

No known drug allergies

FAMILY HISTORY

Sister – breast cancer

SOCIAL HISTORY
No tobacco or alcohol use

PHYSICAL EXAM
Examination revealed erythematous and eroded papules and plaques over the mons pubis, perineum, and gluteal cleft. Maceration and scattered erosions were appreciated in the inguinal folds and pannus. The left axilla revealed scattered erythematous papules and small focal erosions and maceration. Her right axilla was clear.

There was no palpable inguinal, axillary, cervical, or supraclavicular lymphadenopathy.

HISTOPATHOLOGY
Histopathology (2016) demonstrated a diffuse interstitial inflammatory infiltrate of histiocytes admixed with plasma cells and eosinophils. The infiltrate abutted the epidermis with no appreciable Grenz zone. The histiocytes stained positively for CD1a, CD207 (Langerin), and S100.

B-RAF testing - negative

LABORATORY RESULTS
Complete blood count with differential and complete metabolic panel were unremarkable.

DIAGNOSIS
Adult Langerhans Cell Histiocytosis

TREATMENT AND COURSE
Given the worsening and rapid progression of her disease after completing a 1-year course of vinblastine, dermatology and hematology decided to start the patient on methotrexate. She was started on 10 mg weekly and this was subsequently increased to 20 mg weekly. The patient is following up with RUSH dermatology and hematology later this month.

DISCUSSION
The first classification system for histiocytoses was developed in 1987, and since that time more than 100 subtypes have been described. The most recent revision classifies histiocytoses into 5 groups: (1) Langerhans-related; (2) cutaneous and mucocutaneous; (3) malignant histiocytosis; (4) Rosai-Dorfman disease; and (5) hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

Our patient falls into the first group, Langerhans-related. This group includes LCH, Erdheim-Chester disease, and extracutaneous juvenile xanthogranuloma. Many cases within this group have activating mutations in mitogen-activated protein kinase or MAPK pathways. B-RAF testing should be performed in all patients, as inhibitors of this pathway have important treatment implications in these diseases.

LCH is observed more often in the pediatric population making adult-onset LCH exceedingly rare, with an estimated prevalence of only 1 or 2 cases per million. LCH is characterized by an abnormal proliferation of histiocytes within one or more organ systems. Though it can involve any organ, adult-onset LCH most commonly involves the skin, bones and lungs.

When limited to the skin, adults typically have disease in the genital as well as head and neck regions. Cutaneous manifestations, however, are highly variable with features that may mimic chronic eczema, inverse psoriasis, fungal infection, or another non-specific dermatitis. Petechial hemorrhage can be a useful clinical clue to aid in the diagnosis of LCH. Lung involvement may be asymptomatic in adults with LCH and smoking cessation is an important intervention for patients. The pathogenesis of LCH remains unclear, however, demonstration of clonality on immunohistochemical analysis as well as the occasional presence of activating B-RAFV600E mutations suggests that the disease may represent a neoplastic process.

Given the wide variety of clinical presentations and the ability for LCH to affect multiple organ systems, a comprehensive workup should be pursued to screen for systemic disease. A complete blood count with differential, hepatic function studies, urinalysis, coagulation studies, thyroid function tests, CT of the chest, abdomen, pelvis, and full skeletal X-rays should be obtained. All of these tests were unremarkable in our patient. Immunohistochemical analysis showing positivity for CD 207 (Langerin), CD1a, and S100 protein is often needed to confirm the diagnosis. Positive staining for CD207 (Langerin) can distinguish between LCH and other indeterminate S100-positive histiocytoses, including Rosai-Dorfman disease.

LCH can often prove very resistant to therapy, as is the case with our patient. With minimal and isolated skin involvement, topical steroids may be all that is required. However, with extensive and highly symptomatic disease, patients may require systemic corticosteroids, nitrogen mustard, narrowband UVB, PUVA, methotrexate, or thalidomide. For multi-system disease or refractory cutaneous disease, chemotherapy with vinblastine is considered first-line therapy. B-RAFV600E mutation analysis should be performed to investigate whether Imatinib or other tyrosine kinase inhibitors may be beneficial in a patient's treatment.

Since our patient's BRAF testing was negative, she was treated with vinblastine and although significant improvement occurred after completing a 12-month course of therapy, she had prompt recurrence of her disease on discontinuation of chemotherapy. This case highlights challenges with LCH including a variable clinical presentation and disease recurrence since definite treatment has not yet been achieved.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 7**

Presented by Samantha Barry, MD, MS, Mark D. Hoffman, MD and Claudia Hernandez, MD
Department of Dermatology, RUSH University Medical Center

PATIENT A

HISTORY OF PRESENT ILLNESS
A 62 year old black woman presented to RUSH Dermatology in 2015 with recurrent lesions on the back of the neck, axillae, pannus, and inguinal folds for 50 years. Lesions were itchy and intermittently drained serosanguinous fluid. She carried a diagnosis of Hailey-Hailey Disease (HHD) from an outside dermatologist. She had been stable on doxycycline 100 twice daily, benzoyl peroxide gel and clobetasol ointment, but after running out of refills had begun to flare.

PAST MEDICAL HISTORY
Hypertension
Hyperlipidemia
Obesity

MEDICATIONS
Atorvastatin
Olmesartan
Hydrochlorothiazide
Aspirin
Cetirizine

ALLERGIES
Penicillin
Sulfa

FAMILY HISTORY
Daughter – HHD
Son – HHD

SOCIAL HISTORY
No tobacco use

PHYSICAL EXAM
Posterior neck, inframammary folds, axillae, pannus, inguinal folds with erythematous, macerated thin plaques with paper thin linear fissuring, many with superimposed crusting.

HISTOPATHOLOGY
Biopsy of the left thigh demonstrated hyperplasia of the epidermis, suprabasilar clefting, and acantholytic cells.

LABORATORY RESULTS
None

RADIOLOGY
None

TREATMENT AND COURSE
On initial presentation, the patient was restarted on doxycycline, benzoyl peroxide gel, as well as clobetasol ointment. Over the course of two years, the patient's disease waxed and waned. Other treatment options including bleach baths, topical formulations of clindamycin and gentamicin, econazole, pimecrolimus, betamethasone, and oral minocycline. The patient had minimal improvement with numerous relapses. She was started on naltrexone 4.5 mg daily and at follow-up 4 months later, the patient reported near complete clearance of her HHD. While on naltrexone she reported no recurrences but when the patient discontinued it there was disease recurrence at all previously involved sites.

PATIENT B

HISTORY OF PRESENT ILLNESS
A 50 year old black woman presented to RUSH Dermatology in 2016 for recurrent lesions in the axillae, groin, and abdominal folds for 35 years. The lesions were painful and intermittently drained fluid. She was being treated by an outside dermatologist with cefadroxil and vinegar soaks without improvement.

PAST MEDICAL HISTORY
Hypertension
Hyperlipidemia
Chronic kidney disease on dialysis s/p failed kidney transplant
Sleep apnea
Obesity

MEDICATIONS
Furosemide
Tacrolimus
Mycophenolate
Prednisone
Famotidine
Evolocumab
Calcium carbonate
Calcitriol

ALLERGIES
Iron
Statin

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
No tobacco use

PHYSICAL EXAM
Axillae and abdominal folds demonstrated well-demarcated erythema with central maceration and scattered erosions, and fissures.

HISTOPATHOLOGY
Biopsy of the right axilla demonstrated acantholytic dyskeratosis.

LABORATORY RESULTS
None

RADIOLOGY
None

TREATMENT AND COURSE
The patient was diagnosed with HHD, and continued to follow with RUSH Dermatology for two years. Treatment with clindamycin lotion, gentamycin ointment, fluticasone ointment, doxycycline and NB-UVB therapy were tried with minimal success. She was started on naltrexone 3 mg daily, with the approval of her transplant team. After 1 month, she returned with significant improvement. Her dose was increased to 4.5 mg daily. Two months later, her HHD in the inframammary folds remained clear but involvement of both axillae had worsened.

DIAGNOSIS
Hailey-Hailey Disease

DISCUSSION
HHD, also known as Familial Benign Pemphigus, is a heritable disorder characterized by waxing and waning vesicular and erosive lesions that primarily affect intertriginous areas. It is due to a defect in *ATP2C1* that causes abnormal intracellular calcium signaling leading to loss of cellular adhesion in the stratum spinosum. Although not life threatening, HHD morbidity is significant due to disease chronicity and recurrences. Areas of HHD can become secondarily infected, rare cases of malignant transformation have occurred, and some patients may experience depression. Many patients can be managed conservatively with topical medications including steroids and antimicrobials. While these therapies do not appear to impact recurrence rates, they can ameliorate symptoms associated with developing lesions. Other therapies for more refractory cases include botulinum toxin, laser therapy, topical calcineurin inhibitors, and oral retinoids. Despite a variety of treatment options, HHD often remains difficult to control with poor sustained remissions.

Recently, the use of low dose oral naltrexone has been described. Dosages have varied from as low as 1.5 mg to 4.5 mg daily. Early study results have been promising, showing a rapid reduction in symptoms over the course of one to two weeks, leading to clinical remission within two months. Patients showed an improvement of at least 80% in healing of erosions, pain, and subjective quality of life within two to three months. Furthermore, symptoms flared after discontinuation of naltrexone followed by clearance upon re-challenge with naltrexone in 2-3 days, suggesting that naltrexone monotherapy, in some instances, is sufficient to control disease.

The following table lists published reports of naltrexone use in HHD and its effect. Due to the rarity of this genodermatosis, initial studies were limited to a handful of patients.

PUBLICATION TYPE	NUMBER OF PATIENTS	DAILY NALTREXONE DOSE (MG)	EFFECT
Case report	**1**	**4.5**	**Improved**
Brief report	**3**	**1.5-3.0**	**All improved**
Case report	**1**	**4.5**	**Improved**
Research letter	**3**	**4.5-12.5**	**2 improved, 1 with persistent flares**

At this time naltrexone's mechanism of action is not understood. It is a long-lasting opiate receptor antagonist that modifies the perception of pruritus. Higher doses (50 mg) have been used to treat diseases with associated itch such as chronic renal failure, cholestasis or liver cirrhosis. Low dose naltrexone (4.5 mg) only blocks opiate receptors temporarily leading to increases in B-endorphin. This affects pain perception and leads to increased endocrine secretion from the hypothalamus. The exact mechanism remains unclear. Low dose naltrexone may also exert anti-inflammatory effects by antagonizing toll-like receptor 4 but this has yet to be proven. Downstream signaling pathways of TLR-4 have been implicated in calcium homeostasis. For Hailey-Hailey disease, this is important because it may lead to increased cellular adhesion.

These two cases are presented as additional examples of the variable response of HHD to low dose naltrexone. Larger, long term studies are needed to determine if naltrexone produces consistent, sustainable HHD disease remissions.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 8**

Presented by Neal Kumar, MD and Claudia Hernandez, MD
Department of Dermatology, RUSH University Medical Center

PATIENT A

HISTORY OF PRESENT ILLNESS

A 47 year old female with no significant past medical history was transferred to RUSH from an outside hospital for acute respiratory distress unresponsive to antibiotics. She first noticed the acute onset of bilateral finger swelling and a tender palmar rash four months earlier. The patient went to urgent care and was given unknown topical creams that resulted in no improvement. A few weeks later she went back to urgent care for evaluation of a dry cough. She was given benzonatate perles as well as albuterol and reported that her cough improved. However the finger swelling, rash, and pain did not. Her PCP evaluated her one month later and treated her with multiple courses of prednisone, up to 60 mg daily, with some improvement of her finger swelling.

In the month leading to her presentation at RUSH, the dry cough recurred and rapidly progressed until she developed significant shortness of breath. The patient presented to an outside hospital where a chest radiograph showed multifocal infiltrates. Despite treatment with various antibiotics for a presumed pneumonia, she became progressively hypoxic and was transferred to RUSH. A chest CT revealed multifocal consolidation and ground glass opacities in both lungs. Dermatology was consulted to evaluate the palmar lesions and recommended myomarker panel testing.

MEDICATIONS

Mycophenolate mofetil
Tacrolimus
Prednisone
Sulfamethoxazole-trimethoprim

PHYSICAL EXAM

Bilateral palmar interphalangeal joints and distal thumbs revealed ill-defined red to violaceous papules and plaques, some with focal central hyperkeratotic ulcerations. Her face, chest, back, and periungual digits were clear. No scalp alopecia was noted.

LABORATORY RESULTS

LABORATORY TEST	RESULT	REFERENCE RANGE
MDA-5 (P140) (CADM-140)	**>150 (Strong Positive)**	< 20
Anti-SS-A 52 kD Ab, IgG	**97 (Positive)**	< 20
Rheumatoid factor	**71 IU/mL**	0-29 IU/mL
Anti dsDNA	6 IU/L	0-26 IU/L
Anti-RNP and anti-Sm	0.26	0-0.9
Anti-Sm	0.08	0-0.9
SSA	0.06	0-0.9
SSB	0.14	0-0.9
IFA ANA titer	1:40	< 1:40
Aldolase	8.1 U/L	< 8.1 U/L
Ferritin	147 ng/mL	12-260 ng/mL

RADIOLOGY
Chest CT with IV Contrast
IMPRESSION: Multifocal consolidation and ground-glass opacities in both lungs which could represent infection. If the patient does not demonstrate symptoms of infection the possibility of organizing pneumonia should be considered.

PATIENT B

HISTORY OF PRESENT ILLNESS
A 55 year old African-American male with no significant past medical history presented to RUSH with a three week history of shortness of breath, malaise, and weakness. Two weeks prior, he also developed polyarthralgia, joint swelling and asymptomatic, fixed palmar lesions.

He had been evaluated at an outside hospital one week after the onset of shortness of breath where a chest CT, pulmonary angiogram, and bronchoscopy along with lung biopsies were performed. Since he has been on a Caribbean cruise immediately prior to the onset of his symptoms, his infectious work-up included leptospirosis, EBV, CMV, dengue, Zika, chikungunya, HIV, as well as syphilis that were all negative. Repeat chest imaging at RUSH showed diffuse ground glass opacities and bilateral hilar lymphadenopathy. Dermatology was consulted to evaluate violaceous palmar interphalangeal tender papules and recommended a myomarker panel.

MEDICATIONS
Mycophenolate mofetil
Tacrolimus
Sulfamethoxazole-trimethoprim

PHYSICAL EXAM
Bilateral palmar digits revealed ill-defined non-tender red macules and patches, several with central hyperkeratosis overlying the palmar distal, proximal interphalangeal and metacarpophalangeal (MCP) joints. No alopecia was noted on the scalp.

LABORATORY RESULTS

LABORATORY TEST	RESULT	REFERENCE RANGE
MDA-5 (P140) (CADM-140)	**53 (Positive)**	< 20
Anti-SS-A 52 kD Ab, IgG	**107 (Strong Positive)**	< 20
Rheumatoid factor	**43 IU/mL**	0-29 IU/mL
Anti dsDNA	15 IU/L	0-26 IU/L
Anti-RNP and anti-Sm	0.11	0-0.9
Anti-Sm	0.08	0-0.9
Smooth muscle antibodies	1:160 **(Positive)**	Negative
SSA	0.00	0-0.9
SSB	0.10	0-0.9
ANA screen	Negative	Negative
Aldolase	7.8 U/L	< 8.1 U/L
Ferritin	**1888 ng/mL**	12-260 ng/mL

RADIOLOGY

CT Chest with IV Contrast

IMPRESSION: Scattered ground-glass opacities in all 5 lobes, likely representing multifocal infection. Reactive mediastinal and hilar lymph nodes.

DIAGNOSIS

Anti-MDA-5 antibody positive dermatomyositis presenting with rapidly progressive interstitial lung disease

DISCUSSION

Dermatomyositis (DM) is a systemic autoimmune disease characterized by variable involvement of the skin, muscle, and lung.

Approximately 60-70% of patients with DM have detectable myositis-associated (MAAs) or myositis specific- antibodies (MSAs), which may be helpful for risk stratification and prognosis. MDA-5 is the autoantigen recognized by the anti-CADM-140 antibody, and functions as an RNA helicase. MDA-5 is unique among the DM-specific autoantigens in terms of its cellular localization and function. Unlike some of the other DM-specific antigens (p155 or Mi-2), which are nuclear proteins involved in transcriptional or translational regulation, MDA-5 localizes to the cell membrane. It senses intracellular viral infection and subsequently upregulates type I interferons to suppress viral replication and modulate adaptive immunity.

Anti-MDA-5 antibody positivity, found in ~10-30% of DM patients, can be associated with absent or minimal myositis (amyopathic DM), interstitial lung disease (that may be rapidly progressive), arthritis, hand swelling, and a characteristic cutaneous phenotype consisting of diffuse, non-scarring hair loss, skin and oral ulcerations, as well as palmar papules that demonstrate occlusive vasculopathy on histopathology. MCP or interphalangeal joint creases are the most common palmar locations with inflammatory and often tender macules or papules that can appear pale, atrophic, erythematous, violaceous, or ulcerated.

Table 1. Clinical features of anti-MDA-5 dermatomyositis

LESION	DISTRIBUTION	PREVALENCE, %
Cutaneous ulceration	MCP, IP joints, elbows, knees, nail folds	40-82
Alopecia	Scalp, typically diffuse, non-scarring	78
Lateral digit hyperkeratosis	Thenar and lateral aspects of fingers	67
Palmar papules	Palms, palmar creases of fingers	20-60
Oral ulcers	Gingiva, buccal mucosa, tongue, palate	50
Panniculitis	Upper arms, thighs, breasts, buttocks	20

Adapted from Kurtzman D, Vleugels R. Anti-melanoma differentiation-associated gene 5 (MDA5) dermatomyositis: A concise review with an emphasis on distinctive clinical features. J Am Acad Dermatol. 2018 Apr;78(4):776-785.

Although seropositivity to MDA-5 antibodies can be an important diagnostic marker; the prognosis, treatment response, risk of relapse, and risk for malignancy are ill-defined. While the association between dermatomyositis and malignancy is well established, this remains unclear with the MDA-5 subtype given its recent recognition and rarity. There are isolated reports of malignancy occurring in this subtype, yet most case observations and series indicate a reduced risk for malignancy. No malignancies have been detected in either of our patients.

Studies also suggest that serum ferritin levels correlate with disease activity, particularly ILD. Patient A with normal ferritin levels was observed to respond well to therapy resulting in well controlled lung disease. Patient B, whose ferritin was initially elevated to 1,888 ng/mL [reference range: 12-260 ng/mL], has had progressive lung disease despite similar therapy, and is now on the lung transplantation list.

Studies have reported that anti-MDA5 antibody levels may correlate with disease activity and predict who is at risk for relapse of interstitial lung disease. Matsushita reported a decrease in serum anti-MDA5 antibody levels in 12/12 patients who achieved clinical remission. In 50% of these patients, detection of anti-MDA5 antibodies actually became negative. Four of the 12 patients had clinical relapse of lung disease, and no significant difference was observed in the level of antibodies at the time of diagnosis between relapsed and non-relapsed patients. However all relapsed patients demonstrated an increase in the antibody levels compared with levels found at the time of remission. Further-more, increase in the index value to > 50 for the antibody level was associated with relapse. Of note Patient B's MDA5 titers were lower at diagnosis (53) compared to Patient A (>150). Yet Patient B has had a much more severe and progressive clinical course. We present these two cases of MDA-5 antibody positive DM to illustrate the unique cutaneous phenotype as well as add our clinical observations to the discussion of the use of ferritin and MDA-5 titers in these patients.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 9**

Presented by Nick Blickenstaff, MD and Morayo Adisa, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

The patient is a 57 year old white man who presented to Rush Dermatology for evaluation of an enlarging lesion on the right upper arm. The lesion was first noted two years prior to presentation as a small subcutaneous nodule which over a year demonstrated accelerated growth, doubling in size while also becoming darker in color. It was tender to palpation and reported to be mildly pruritic. The patient had no personal or family history of melanoma or other non-melanocytic skin cancer and was otherwise healthy. Review of systems was negative for any constitutional symptoms.

PAST MEDICAL HISTORY

None

MEDICATIONS

None

ALLERGIES

No known drug allergies

FAMILY HISTORY

Mother and father - lung cancer

SOCIAL HISTORY

Non-smoker

PHYSICAL EXAM

A 2.6 cm x 1.5 cm reddish-blue nodule surrounded by roughly 1 cm of induration on the right mid upper arm. The lesion was tender to palpation. No palpable cervical or axillary lymphadenopathy.

HISTOPATHOLOGY

The lesion is a large dermal epithelial neoplasm surrounded by a thick capsule of fibrous tissue with areas of hemorrhage and granulation tissue. The tumor is comprised of basaloid cells with a biphasic cell population of outer layer cells with small hyperchromatic nuclei, minimal cytoplasm, and surrounding larger cells with round or oval vesicular nuclei and more conspicuous eosinophilic cytoplasm that are arranged partly in trabeculae and cohesive aggregates with ductal differentiation.There is eosinophilic secretory material in the lumina and cystic degeneration of the tumor. The tumor shows a spectrum of changes ranging from benign spiradenoma to a spiradenocarcinoma with areas of necrosis, frequent mitotic figures, infiltrative growth pattern and loss of the biphasic cellular population.

LABORATORY RESULTS

None

DIAGNOSIS

Low grade spiradenocarcinoma

TREATMENT AND COURSE

The patient was referred to surgical oncology for wide local excision with 1 cm margins and sentinel lymph node biopsy (0/3) from the right axilla. He was subsequently referred to medical oncology to establish care and follows with dermatology every 3-6 months for total body skin exams.

DISCUSSION

Spiradenocarcinomas (SpAds), also referred to as malignant eccrine spiradenomas, are rare and potentially aggressive skin adnexal tumors. Only 121 cases of SpAds have been published in the medical literature, mainly as case reports, resulting in great variability with the published data. Although traditionally regarded as high-grade malignancies, recent studies have demonstrated that cellular morphology is a good predictor of clinical outcome. Morphologically high-grade tumors are associated with an aggressive disease course with high rates of local recurrence, distant metastases and mortality. In contrast, low grade tumors tend to follow an indolent clinical course. A benign preexisting eccrine spiradenoma is considered the primary skin lesion from which SpAd evolves, but de novo development has been reported.

SpAds present as solitary nodules with a median size of 3-4 cm in diameter. Reported anatomic distributions are broad with a predilection for the head and neck areas. SpAds occur predominately in elderly patients (median age 60 years), however, a wide range in patient ages have been reported from as young as 8 up to 92 years. There is no gender predilection. Changes or symptoms that prompt patients to seek medical evaluation are typically accelerated growth of a long-standing lesion, pain, and/or ulceration. Bluish discoloration and impairment resulting from tumor growth have also been described. Although the majority of tumors are sporadic, they have also been reported to occur in patients with Brooke-Spiegler syndrome.

The diagnosis of SpAd rests on finding the necessary histopathological findings. Low-grade tumors often arise in a pre-existing spiradenoma, and demonstrate loss of dual cell population, diffuse growth of monotonous cells, mild to moderate cytologic atypia, and increased mitotic activity. High-grade tumors are characterized by unilobular or multilobular tumor mass(es) composed of sheets of pleomorphic epithelial cells. The tumors display an infiltrative growth pattern and may invade deeply. The mitotic count is high and tumor necrosis is frequently seen. Specific tumor markers for SpAd have not been identified yet.

A comprehensive review by Staiger et al. determined that tumor grading was reported in only 30% (36/121) of all cases, with low-grade SpAds reported over three times more frequently. Their data also supported a higher incidence of tumor recurrence (50% vs 14%) and death (38% vs 14%) in high-grade SpAd versus low-grade cases. Metastatic spread was seen in 19% (23/121) of patients, most commonly to the lymph nodes, bone, and lung. Preoperative investigations were rarely documented and consisted mostly of CT scans or MRI for determination of the extent of tumor infiltration. Unfortunately there is no data or consensus statement on the optimal management strategy for patients with metastatic disease. Tumor resection was the primary intervention for all patients. Regional lymph node excision should be performed for tumor positive regional lymph node cases and sentinel node biopsy considered in clinically unsuspicious ones.

In addition to tumor resection, adjuvant radiotherapy and chemotherapy has been reported in 6 patients. Three patients received adjuvant radiotherapy, one of them in combination with chemotherapy. Four patients underwent adjuvant chemotherapy. Agents used were 5-fluorouracil, Tamoxifen, Epirubicin, and Ifosfamide. Meta-analysis with Kaplan–Meier survival

curves demonstrated a poor prognosis in metastatic disease with a median survival time of 20 months. Patient survival did not significantly differ between local resection and adjuvant chemoradiotherapy with surgical removal of tumor burden. Prospective collection and reporting of cases is needed to further elucidate treatment regimens of SpAd.

This patient is an example of a rare low grade SpAd arising in a spiradenoma. Strong consideration should be given to excising longstanding and enlarging spiradenomas given the potential association with SpAds. Due to the more aggressive behavior seen in high-grade SpAds, emphasis should be placed on determination of tumor differentiation grade to aid in assessing prognosis. Complete tumor excision and sentinel lymph node biopsy should be performed with resection of tumor involved lymph nodes in an attempt to reduce the risk of metastatic disease. Patients diagnosed with SpAd should receive regular follow-up by an interdisciplinary team of dermatologists and medical oncologists.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 10**

Presented by Samantha Barry, MD, MS and Claudia Hernandez, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 60 year old black woman presented for evaluation of a toenail lesion on the first digit of her right foot. The lesion initially presented 5 years ago as a faint brown longitudinal streak. Over time the streak became progressively wider and darker but remained asymptomatic. She was told that the streak represented a fungal infection and was prescribed a topical antifungal cream. She did not fill the prescription due to the cost of the medication. The lesion continued to progress and 4 months prior to presentation to dermatology, her toenail split, began to bleed and crust. Two months prior to presentation she noticed the appearance and rapid growth of a red, enlarging mass with cloudy foul smelling drainage near the proximal nailfold. She was unable to have the biopsy performed by podiatry, reportedly due to insurance issues, and presented to RUSH Dermatology for evaluation.

PAST MEDICAL HISTORY

Breast cancer status post lumpectomy, estrogen receptor/progesterone receptor positive

MEDICATIONS

Anastrozole

ALLERGIES

No known allergies

FAMILY HISTORY

Father: prostate cancer
Grandmother and cousin: cervical cancer
No family history of skin cancer or melanoma

SOCIAL HISTORY

None

PHYSICAL EXAM

Right foot, first digit: 15 mm x 8 mm ulcerated red tumor near the proximal nailfold. The nail was dystrophic with visible irregular dark brown/black pigmentation immediately adjacent to tumor. Cloudy, foul smelling fluid was observed weeping from the base of the mass
No palpable lymphadenopathy of the popliteal, inguinal, or axillary nodes.

HISTOPATHOLOGY

A. Skin, right great toe, proximal nailfold, superficial; biopsy: Invasive melanoma, at least 3.2 mm in thickness, ulcerated.

B. Skin, right great toe, proximal nailfold, deep; biopsy: Invasive melanoma.

MELANOMA SUMMARY
Tumor thickness (Breslow depth): At least 3.2 mm
Anatomic (Clark) level of invasion: At least IV
Ulceration: Present, diffuse
Histologic type: Acral, nodular
Mitotic rate: 8/mm2
Lymphovascular Invasion: Not identified
Neurotropism: Not identified
Regression: Not identified
Tumor-Infiltrating lymphocytes: Present, focally brisk
Associated nevus: Not identified
Margins: Positive deep and peripheral margins
Pathologic Stage (pTNM, AJCC 8th Edition): at least PT3bNxMx

RADIOLOGY

Right first digit radiograph: negative for cortical destruction or periosteal reaction with moderate hallux valgus with associated degenerative change

Ultrasound, right groin: Prominent but non-enlarged right inguinal lymph nodes.
CT Chest, abdomen and pelvis:
1. Enlarged left thyroid lobe with nodule.
2. Few pulmonary micronodules of indeterminate significance.
4. Left upper inner asymmetric breast density with adjacent surgical clips.

DIAGNOSIS

Acral Melanoma, nodular type

TREATMENT AND COURSE

At the time of CDS protocol submission, a right great toe amputation and sentinel lymph node biopsy had been performed by Surgical Oncology. Further treatment decisions are pending.

DISCUSSION

Cutaneous melanoma is considered a preventable and potentially curable disease. Although melanoma is more prevalent in non-Hispanic Whites (referred to as Whites), Blacks, and Hispanics have recently been identified as presenting with more advanced stage disease. Early diagnosis is crucial since melanoma prognosis is directly related to tumor stage, with thicker lesions having less favorable outcomes. While early recognition and prognosis of melanoma as a whole has improved, some rarer forms need increased attention. Among them are acral melanomas that arise on the palms, soles, and nail beds. Cutaneous melanoma has commonly been classified into four major histologic types: superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma and acral lentiginous melanoma (ALM). Although ALM affects all ethnicities, it is the most common subtype of melanoma that affects non-white populations. It accounts for 10% of melanoma cases in Whites but more than 60% of cases in non-white populations.

Epidemiological data indicates melanoma risk factors include presence of multiple nevi, history of chronic/intermittent sun exposure, as well as white skin type however, these

factors do not appear strongly related to acral melanoma. The role of acral nevi in the development of ALM also remain unclear since it is extremely rare for there to be a preexisitng nevus at the site of an acral melanoma. However, mechanical stress or a history of trauma has been associated with the risk of melanoma development on acral sites.

Melanoma is a highly mutated malignancy in large part as a function of ultraviolet light, a known carcinogen, and/or other mutational exposures. Melanomas from different body sites differ in the degree of ultraviolet radition (UVR) exposure and some of the variability in mutations can be attributed to its presence or absence. Molecular studies have identified recurrent mutations in BRAF (45-60% of cases) and NRAS (15-25%). These mutations are mostly present in intermittent or chronically sun-exposed sites and are often classified as LMM or SMM. Whole exome/genome studies have found differences between UVR-related melanoma and non-UVR-related melanomas on the mucosa, palms, soles and nails. Although mutations more commonly seen in UV-related melanoma can be seen in a small number of acral melanomas, some unique molecular features include a low mutation burden, point mutations in genes including *KIT*, and recurrent genomic copy alterations in *CCND1*, *AURKA*, and *TERT* genes. This supports the belief that there is a different causal pathway between UVR exposure related melanomas and non-UVR derived melanomas. It has been suggested that poorer outcomes with ALM are the results if its unique molecular biology that results in more aggressive disease.

Published data suggests that ALM has a worse prognosis when compared to other melanoma subtypes. A recent publication of a large series of ALM cases by Teramoto et al. in 2017 found that it had the same prognostic indictors as other subtypes of melanoma suggesting once again that unfavorable prognosis is likely primarily driven from diagnostic delays. Despite their lower melanoma rates, Hispanics and African-American Blacks are more likely to have a delayed diagnosis as compared to Whites. Thus, the proportion of later stage melanomas is greater in African-American Blacks as compared to Whites. This directly leads to differences in survival across races, with Whites having a significantly better melanoma-specific 5-year survival rate (82.6%) as compared to African-American Blacks (77.2%), Hispanics (72.8%), and Asians (70.2%), as noted in the SEER population-based data registry from 1986-2005.

Barriers related to poverty, insurance status (dependence of government sponsored programs), decreased access to quality dermatologic care, and lack of awareness about melanoma appear to disproportionately affect racial and ethnic minorities and likely play a role in diagnostic delays and poor outcomes. The rarity of this melanoma subtype in these populations adds to the difficulty and complexity of unraveling the role of social inequities in melanoma outcomes. They remain an important area to investigate if our specialty is to assist with the development of effective interventions that improve early detection and prevention of acral melanomas.

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