Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, May 5, 2021
Online via Zoom

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

Program

Host: Rush University
Wednesday, May 5, 2021
Online Conference

8:30 a.m.	**Sign-in and Member Visitation Time**
9:00 a.m.	**Welcome & Introduction** *David Mann, MD - CDS President*
9:05 a.m. - 10:00 a.m.	**Guest Lecture #1** "Vitiligo: Clinical Characteristics, Optimizing Management, and Emerging Treatments" *John E. Harris, MD PhD*
10:00 a.m. - 10:45 a.m.	**Resident Case Presentations & Discussion** Rush University *Residents*
10:45 a.m. - 11:00 a.m.	Questions
11:00 a.m. - 11:30 a.m.	**Guest Lecture #2** "Disorders of Hypopigmentation Kodas: What Is Vitiligo, and What's Not?" *John E. Harris, MD PhD*
11:30 a.m. - 12:00 p.m.	**Case Discussion**
12:00 p.m.	**Closing Remarks – Meeting Adjourns** *David Mann, MD*

Mark the Date!

The 2021 President's Meeting is scheduled for Wednesday, June 2. Watch the CDS website for details, coming soon.

Guest Speaker

JOHN E. HARRIS, MD PHD

Chair, Department of Dermatology;
Professor of Dermatology;
University of Massachusetts Medical School
Worcester, MA

Dr. Harris is chair of the Department of Dermatology and is a Professor of Dermatology at the University of Massachusetts Medical School (UMMS) in Worcester. He directs the Vitiligo Clinic and Research Center at UMMS which incorporates a specialty clinic for the diagnosis and treatment of patients with vitiligo, as well as a vitiligo research laboratory.

Dr. Harris earned both his MD and PhD degrees at the University of Massachusetts, with his doctoral thesis focused on the loss of autoimmune tolerance in juvenile diabetes. He then entered a combined research/residency program in dermatology at the University of Pennsylvania in Philadelphia. Dr. Harris has authored multiple research publications and textbook chapters on vitiligo and other topics, and he serves on a number of advisory boards and committees, including the Dermatology Foundation, the American Academy of Dermatology, and the New England Dermatology Society, among others. He is an ad hoc reviewer on grant applications for the National Institutes of Health and the National Alopecia Areata Foundation, as well as multiple research journals.

CME Information

May 5, 2021

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 typically schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. Two lectures are given by the guest speaker, and the residents of the host institution present cases which are offered for audience discussion. During the coronavirus pandemic, CDS has continued to organize our regular educational conferences, but in a half-day "virtual" online live setting.

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 May 2021 meeting, the participant should be able to:
1. Describe the clinical characteristics, optimizing management and emerging treatments for patients with vitiligo.
2. Discuss disorders of hypopigmentation kodas.
3. List the factors that would differentiate vitiligo from other hypopigmentation discorders.

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 3 *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 an online CME claim form after the completion of the conference. A link to this form along with the online evaluation form will be sent to each conference attendee after 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. The guest speaker, Dr. John Harris has disclosed certain potential conflicts of interest which are displayed on the next page. Dr. Harris also has stated he does intend to discuss off-label use of commercial products or devices. None of the other participants in this conference have disclosed relevant potential conflicts of interest.

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

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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.

Disclosures: John Harris MD PhD; May 2021

Name	Consultant	Investigator
Pfizer	X	X
Genzyme/Sanofi	X	X
Incyte	X	X
Rheos Medicines	X	X
Sun Pharmaceuticals	X	X
LEO Pharma	X	X
Villaris Therapeutics, Inc.	X	X
Dermavant	X	X
TeVido BioDevices	X	X
Temprian Therapeutics	X	
AbbVie, Inc	X	
Janssen	X	
Almirall	X	
Methuselah Health	X	
Pandion	X	
AnaptysBio	X	
Avita	X	
NIRA Biosciences	X	
Admirx	X	
Equity: TeVido Biodevices, Rheos, Villaris Therapeutics, Inc., NIRA Biosciences		
Founder: Villaris Therapeutics, Inc., NIRA Biosciences		

Case Presentations

Rush University
Residents

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 1

Presented by Ryan Kelm, MD, Kevin Cavanaugh, MD
Division of Dermatology, RUSH University Medical Center

UNKNOWN

CHICAGO DERMATOLOGICAL SOCIETY

CASE 2

Presented by Nour Al-Hadidi, MD, Luke Wallis, MD, Warren Piette, MD
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 78-year-old female was referred to Rush University Medical Center after biopsies of two lesions on the right lower extremity were read as squamous cell carcinoma (SCC). Three years prior, she was treated for a SCC of the right lower leg with radiation therapy. She reported new lesions on her right leg present for at least six months. On exam, the patient had two healing biopsy sites, one cm each, surrounded by keratotic papules and plaques concerning for in-transit metastases. With these findings, the patient was referred to surgical, radiation, and medical oncology. She was deemed a poor candidate for surgery and radiation, given the extent of disease and comorbidities. Instead, the patient was started on cemiplimab by medical oncology for treatment of recurrent unresectable SCC.

Three weeks following initiation of cemiplimab, the patient developed a rash involving the arms, chest, and thighs characterized by erythematous patches with overlying scale, as well as an increase in size of the plaques on her right leg. Following additional infusions, the plaques on the right lower extremity progressed to painful ulcerations, and she was noted to have developed ulcerations on the left lower extremity as well. The patient was admitted to the hospital at which time a biopsy of the rash involving her left thigh was performed. The biopsy revealed lichenoid dermatitis with necrotic keratinocytes and eosinophils. Direct immunofluorescence was negative. She was treated with a potent topical steroid to the affected areas and with systemic antibiotics given the concern for superinfection. The patient initially improved; however, findings again recurred following her fifth infusion of cemiplimab. At this time, an additional biopsy of the rash from the upper back again demonstrated lichenoid dermatitis.

Given these findings, the outside pathology from the patient's initial right lower extremity biopsies was reviewed: one biopsy site demonstrated an atypical squamous proliferation consistent with SCC, while the other showed an atypical squamous proliferation with prominent lichenoid tissue reaction. With clinical pathologic correlation, we felt the best explanation for the patients course was the development of lesions of hypertrophic lichen planus (HLP) six months prior to her presentation to us followed by a generalized cemiplimab-induced lichenoid dermatitis and exacerbation of her underlying lower extremity HLP, which was complicated by histopathologic findings of SCC and keratoacathomas.

PAST MEDICAL AND SURGICAL HISTORY

Squamous cell carcinoma of the right lower extremity s/p XRT
Squamous cell carcinoma of the left lower extremity s/p surgical excision
Hypertension
Hypercholesterolemia

MEDICATIONS

Aspirin 81 mg daily
Vitamin E 400 units daily
Metoprolol XL 25 mg daily
Rosuvastatin 10 mg daily

Amlodipine 5 mg daily
Irbesartan-hydrochlorothiazide 300-12.5 mg daily
Lorazepam 0.5 mg PRN
Prochlorperazine 10 mg PRN

PHYSICAL EXAM

Initial Exam: Two healing biopsy sites, 1 cm each, surrounded by keratotic papules and plaques concerning for in-transit metastases.

Three weeks following cemiplimab: Erythematous annular to ovoid macules as well as patches with overlying scale involving the chest, arms and thighs. Right leg with violaceous edematous plaque.

Exam after 5th infusion of cemiplimab: Erythematous annular to ovoid macules and patches with overlying scale involving the chest, arms, and thighs. Bilateral lower extremities with extensive erosions progressing into ulcerations. Few dome shaped keratotic papules on the right thigh and leg.

PERTINENT LABS/IMAGING

CT C/A/P:
1. No evidence of metastatic disease in the chest, abdomen, and pelvis.
2. Slightly nodular hepatic contour, which could be within normal variation or possible hepatocellular disease (no history of liver disease per the electronic medical record). Correlate with liver function test.
3. Small hiatal hernia. Cholelithiasis. Hysterectomy. Colonic diverticulosis.

CBC with differential: WBC (8.62 K/uL); Hgb (12.5 g/dL); PLT (175 K/uL); Differential (10.1% monocytes, 11.8% Eosinophils).

CMP: Within normal limits except the following: Albumin (3.3 g/dL); Total bilirubin (1.4 mg/dL)

HISTOPATHOLOGY

Biopsy of rash on thigh:

- Specimen A (left anterior thigh superior): Vacuolar alteration of the basal cell layer and a lichenoid inflammatory cell infiltrate containing scattered eosinophils. Necrotic keratinocytes are present within the epidermis.
- Specimen B (left anterior thigh inferior): Vacuolar alteration of the basal cell layer and a lichenoid inflammatory cell infiltrate containing scattered eosinophils; focal hyperkeratosis, hypergranulosis, and epidermal hyperplasia.
- Specimen C (DIF; left anterior thigh perilesional): Immunofluorescence stains for fibrinogen, C1q, C3, IgA, IgM and IgG are essentially negative within the epidermis, at the dermoepidermal junction and around the dermal blood vessels.

Biopsy of rash on back:

- Back: There is parakeratosis with plasma, neutrophils and bacterial colonies. There is epidermal spongiosis with exocytosis and scattered necrotic keratinocytes. A superficial perivascular predominantly lymphocytic infiltrate is present. Lichenoid dermatitis with surface excoriation and impetiginization.

Review of initial RLE biopsies:

- Right anterior lower leg (Site A): Atypical squamous proliferation consistent with surface of well-differentiated squamous cell carcinoma, keratoacanthoma pattern.
- Right anterior lower leg (Site B): Atypical squamous proliferation and lichenoid tissue reaction.

DIAGNOSIS

Cemiplimab-induced lichenoid dermatitis in a patient with atypical squamous proliferations

TREATMENT AND COURSE

Following diagnosis, cemiplimab was discontinued after five total infusions and the patient was treated with prednisone, acitretin 25 mg daily, and wound care with significant improvement in ulcerations and clinical regression of keratoacanthomas.

DISCUSSION

Cemiplimab, a human monoclonal antibody which targets PD-1, is approved for the treatment of advanced and metastatic cutaneous SCC. The high mutation burden of cutaneous SCCs renders them sensitive to effector T cells induced by immune checkpoint inhibitors. In patients treated with cemiplimab, response rate was reported to be ~50%. Dermatologic toxicities are emerging as a consequence of treatment with immune checkpoint inhibitors, including bullous and lichenoid eruptions, vitiligo, and erythema multiforme. The mean time to onset of lichenoid dermatologic toxicity with use of PD-1 inhibitors was 42 days. Among patients treated specifically with cemiplimab, 15% developed rashes; however, these rashes were not further characterized. While most lichenoid eruptions respond well to topical steroids and interruption of immunotherapy may not be necessary, in some cases these reactions may be severe and treatment resistant.

In our patient's case, cemiplimab was used to treat recurrent SCC as diagnosed by an outside pathologist. The patient's unusual clinical course with progression of lower extremity plaques to ulcerations and robust generalized lichenoid dermatitis following initiation of immunotherapy prompted reconsideration of her diagnosis and review of the pathology. While one biopsy site yielded a diagnosis of atypical squamous proliferation consistent with SCC, the other site demonstrated an atypical squamous proliferation with prominent lichenoid tissue reaction consistent with HLP. Clinical and pathologic correlation ultimately led to a diagnosis of HLP with histopathologic findings of SCC and keratoacanthomas.

HLP is a variant of lichen planus characterized by verrucous and hyperkeratotic plaques most commonly involving the lower extremities. Although HLP is considered a benign chronic idiopathic T cell mediated inflammatory disorder, malignant transformation of cutaneous LP has been reported, with an incidence of 0.4%. Most SCC arising in HLP is well differentiated and includes verrucous carcinoma and keratoacanthoma subtypes. An average time interval of 12 years has been documented between the diagnosis of LP and the development of carcinoma. The malignant transformation of LP has been attributed to chronic inflammation and accelerated cellular turnover.

Given the proclivity for SCC to arise within HLP, and the similar clinical features they share, it may be difficult to distinguish between the two diagnoses. Furthermore, histologically, the reactive pseudoepitheliomatous hyperplasia of HLP can be difficult to differentiate from the epidermal hyperplasia in well-differentiated SCC. These similarities have led to several cases, which were initially diagnosed as SCC, to be subsequently classified as HLP upon further

review. Immunohistochemistry and genetic analysis have been proposed as mechanisms to help distinguish the two diagnoses; however, these are not readily available.

While SCC arising in HLP has been treated with various modalities including wide local excision, Mohs micrographic surgery, electrodessication and curettage, radiation therapy and systemic retinoids, one may argue that use of immunotherapy would be contraindicated given inevitable upregulation of T cell mediated immunity which may result in severe dermatological toxicity. Our patient's severe irAE highlights why review of the primary and potential underlying diagnoses is essential in every patient with multiple biopsied squamous neoplasms before any definitive treatment is pursued. We highlight this case to suggest consideration of the diagnosis of HLP in any patient presenting with multiple hyperkeratotic papules on the lower extremities demonstrating squamous atypia on histopathology. Recognizing concurrent HLP may prevent unnecessary excisions in patients thought to have in-transit disease. Furthermore, failure to recognize pre-existing HLP can result in significant morbidity in patients treated with immunotherapy when SCC arises within cutaneous lesions of HLP, or when HLP mimics SCC.

KEY POINTS

- Cemiplimab is approved for the treatment of advanced and metastatic cutaneous squamous cell carcinomas.
- Lichen planus has been described as an irAE secondary to PD-1 inhibitor use.
- Although HLP is considered a benign chronic idiopathic T cell mediated inflammatory disorder, malignant transformation of cutaneous LP has been reported.
- It is difficult to distinguish the pseudoepitheliomatous hyperplasia of HLP from well-differentiated SCC.
- In a patient with multiple, simultaneous, biopsied squamous neoplasms, the primary and possible underlying diagnoses should be reviewed and mimickers considered before any definitive treatment.
- Recognizing concurrent HLP may prevent unnecessary excisions in patients thought to have in transit disease.
- Failure to recognize pre-existing HLP can result in significant morbidity in patients treated with immunotherapy when SCC arises within cutaneous lesions of HLP, or when HLP mimics SCC.

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ABBREVIATIONS AND ACRONYMS

- Programmed death-1 (PD-1)
- Squamous cell carcinoma (SCC)
- Immune-related adverse event (irAE)
- Hypertrophic lichen planus (HLP)
- Lichen planus (LP)

CHICAGO DERMATOLOGICAL SOCIETY

CASE 3

Presented by Luke Wallis, MD, Sarah Ibrahim, BA, Carolyn Stull, MD, Kevin Cavanaugh, MD
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 43-year-old male with no significant past medical history presented with an enlarging skin lesion on his left knee. Originally focal, it progressed to encompass the entire knee, medial leg, and distal thigh over a 10 year period. The patient recently emigrated from Guatemala six months prior to presentation and had worked as a farmer and fork-lift driver. He denied any pertinent previous dermatologic or family history.

The patient described occasional bleeding and pain with ambulation, but otherwise denied fevers, chills, malaise, weight loss, or night sweats. Additionally, he denied any history of injury or trauma to the area. Past treatment with ketoconazole cream and triamcinolone 0.1% cream for an unknown duration did not result in any improvement.

PAST MEDICAL HISTORY

None

MEDICATIONS

Triamcinolone 0.1% cream
Ketoconazole 2% cream

SOCIAL HISTORY

No history of trauma or homelessness

REVIEW OF SYSTEMS

Positive for pain with movement of the knee and ambulation.
Negative for fevers, chills, malaise, weight loss, or night sweats.

PHYSICAL EXAM

Left knee, medial leg and distal thigh – Approximately 30 x 40 cm indurated, verrucous plaque with central scarring, scalloped borders, and overlying adherent white scale.

HISTOPATHOLOGY

Pseudoepitheliomatous hyperplasia and suppurative granulomatous inflammation with multinucleated giant cells, and pigmented copper-colored spores.

PERTINENT LABORATORY RESULTS

Fungal cultures: Velvety, dematiaceous colonies with branched, septated hyphae and erect ovoid to barrel-shaped conidia

DNA hybridization studies performed at a reference laboratory confirmed the species *Fonsecaea pedrosoi*.

DIAGNOSIS

Chromoblastomycosis

TREATMENT AND COURSE

The patient was asked to follow up with infectious disease to begin treatment with itraconazole 200 mg BID. Unfortunately, the patient was lost to follow up.

DISCUSSION

Chromoblastomycosis is a cutaneous and subcutaneous fungal infection caused by melanized fungi, most commonly *Fonsecaea pedrosoi*. It is endemic to tropical and subtropical climates and typically affects adult male agricultural laborers who lack protective clothing. Most commonly, it affects the feet, knees, lower legs, and hands through traumatic inoculation by implantation from an environmental source. Though chromoblastomycosis has been documented in the literature, its presentation in the United States is extremely rare, with fewer than 100 cited cases. Most reports have been primarily localized to Texas and Louisiana and typically affect patients with a history of travel or emigration. Some cases have been sporadically associated with natural disaster. The majority of cases are reported in Latin America, the Caribbean, Africa (specifically Madagascar), and Asia. In the presented case, it is postulated that the patient was likely exposed during his time as a farmer in Guatemala.

Clinically, chromoblastomycosis presents as slow-growing lesions that assume nodular, tumoral, cicatricial, or verrucous morphologies. A significant percentage of surface area can be involved with chromoblastomycosis infection; however, involvement of deep structures is exceedingly rare. Dissemination to the lungs and brain has been sporadically reported, though the most common sequelae are secondary bacterial infection and lymphatic stasis.

The most suggestive finding of chromoblastomycosis on KOH or biopsy is the presence of pigmented muriform cells or “Medlar bodies” which resemble copper pennies. Nonspecific findings include pseudoepitheliomatous hyperplasia and a granulomatous response with giant cells in the dermis. Direct examination of skin scrapings using KOH can aid in diagnosis and will reveal similar muriform cells accompanied by septa and dark hyphae. DNA hybridization can aid in the detection of the most common offending fungal species. Diagnosis of chromoblastomycosis can often be challenging due to difficulty in culturing the organism, rarity of presentation, and the indolent nature of the infection. Differential diagnosis can often include coccidioidomycosis, paracoccidiodomycosis, phaeohyphomycosis, sporotrichosis, verrucous tuberculosis, Bowen’s disease, and/or mycosis fungoides.

Treatment is frequently challenging due to high recurrence rates and the lack of a gold standard therapy. Current accepted strategies rely on oral antifungals. Itraconazole has been the most studied, with recommended dosages between 200 and 400 mg/day for 8-10 months, although cure rates have varied. Terbinafine, dosed between 250 and 500 mg/day, has demonstrated some superiority to itraconazole in the literature due to its comparable efficacy and its few drug-drug interactions.

Chromoblastomycosis is a rarely seen tropical disease that is often treatment refractory most often observed in patients with recent travel to or from endemic locations. Lesions can be clinically indistinguishable from more common conditions, and history is valuable in forming the initial differential diagnosis. Biopsy of lesions with culture must be performed to exclude malignancy, to decrease delays in diagnosis, and to increase likelihood of treatment success.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 4

Presented by Megha Trivedi, MD, Kevin Cavanaugh, MD, Warren Piette, MD.
Division of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 48-year-old Caucasian male with a history of diabetes mellitus type 2, hypertension, and hyperlipidemia presented with multiple indurated papulo-nodules scattered on the face including the eyelids, trunk, bilateral axillae, and groin. The patient reported that the lesions started approximately four years prior on his forehead and neck and then spread to involve multiple other body sites, localizing predominantly to intertriginous areas. He experienced moderate pain, especially when the nodules broke open, and exuded a thick yellow/oily substance.

He denied a personal or family history of skin conditions, but did note that the skin eruption coincided with his diagnosis of diabetes mellitus. He had no history of travel outside of Illinois since age 15 and worked as a concrete worker. He had a biopsy with a dermatologist at the time of onset which confirmed a diagnosis of "xanthomas." Multiple therapeutic modalities including laser therapy and surgical excision were pursued at outside facilities without relief. He reported visual disturbances due to burden of lesions on the eyelids and paresthesia of the lower extremities. He experienced some occasional dyspnea and had a positive history of smoking for 15 years (1ppd). Otherwise, he denied symptoms such as fevers, chills, easy bruising, unintended weight loss, skin tightness, contractures, joint pains, muscle aches, abdominal pain, constipation, diarrhea, or excessive thirst or urination.

PAST MEDICAL HISTORY

Diabetes Mellitus Type 2, Hypertension, and Hyperlipidemia

FAMILY HISTORY

No known family history of cutaneous disease, myeloproliferative syndromes, or autoimmune conditions.

SOCIAL HISTORY

Current smoker, 1 PPD. Consumes alcohol occasionally in social settings. No reported history of recreational drug use.

MEDICATIONS

Atorvastatin, amlodipine, insulin (lispro and glargine)

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Multiple coalescing large red-brown and orange/yellow papulo-nodules, several of which are pedunculated, scattered diffusely on face, affecting eyelids, on neck, axillae, upper

chest, scalp, upper back, and groin. Several areas are eroded (on neck and around eyes) with leaking yellow fluid.

LABORATORY RESULTS

CBC, comprehensive metabolic panel, and urine analysis were largely within normal limits except for glucosuria.
Lipid profile demonstrated hypertriglyceridemia and hypercholesterolemia.
ANA, ANCAs, complements, cryoglobulins were unremarkable.
TSH, CK, and LDH normal
ESR and CRP elevated (61 and 56.2)
SPEP/UPEP/IFE revealed both elevated kappa (3.91) and lambda (3.19) but normal kappa/lambda ratio (1.23)
IgA- (Checked in anticipation for IVIG)- elevated (530)

IMAGING STUDIES

MRI Brain- unremarkable
MRI Spine- Small enhancing lesions within T3/T4 vertebral bodies, likely osseous hemangiomas vs metastases. Otherwise unremarkable.
CXR- unremarkable

DERMATOPATHOLOGY

Histopathologic analysis of two separate punch biopsies taken from the left clavicle and right posterior axilla demonstrated foam cells, histiocytes, touton giant cells, and granulomatous inflammation.

DIAGNOSIS

Xanthoma Disseminatum

CLINICAL COURSE

The patient was referred to multiple sub-specialties given the tendency of XD to involve internal organs including the CNS (diabetes insipidus). An extensive workup was initiated to assess for underlying plasma cell dyscrasia/monoclonal gammopathy and the patient was referred to multiple sub-specialties to assess for internal involvement/CNS involvement despite lack of systemic symptoms. He follows with ophthalmology and plastic surgery/oculoplastic surgery for extensive periocular lesions and there is plan for eventual surgical intervention to reduce disease burden. He is currently being managed conservatively with topical therapies in the periocular region and was also referred to hematology/oncology due to this condition’s association with monoclonal gammopathies/multiple myeloma. At this time there, is no evidence of gammopathy on laboratory evaluation. ENT also evaluated the patient due to possible airway involvement, but this was unremarkable. Due to evidence in the literature of the effectiveness of IVIg for the related condition, NXG, this was attempted as first line therapy. The patient failed to have adequate response after three months of treatment with IVIg. A recent case series in JAMA Dermatology by Khezri et. al, "Xanthoma Disseminatum: Effective Therapy With 2-Chlorodeoxyadenosine in a Case Series" is recent evidence we have for treatments of XD. The patient is currently undergoing

treatment with cladribine with infusions over 5 days repeated every 3-4 weeks with a plan to re-assess after the third cycle.

DISCUSSION

Xanthoma disseminatum is a rare, benign, normolipemic Non-Langerhans cell histiocytic disorder. The condition was first described by von Graefe in 1867 and formally named by Montgomery and Osterberg in 1938. This condition is quite rare with only about 100 cases reported in medical literature. Both children and adults are affected, although the majority of patients are men and have onset of disease before age 25.

Cutaneous disease often presents as an eruption of numerous symmetric yellow, red, and/or brown nodules clustered on the face and intertriginous areas. Xanthomas are not limited to the skin and affect the mucous membranes (upper airway and oral mucosa most commonly) in around 40% of patients. This can lead to mechanical obstruction of the airway causing hoarseness/dyspnea or intestinal blockage presenting with symptoms of small bowel obstruction. Conjunctival and ocular lesions can cause severe morbidity and in some cases, loss or impairment of vision. Approximately 40% of patients develop diabetes insipidus due to involvement of the pituitary fossa presenting with polyuria and polydipsia. CNS involvement has also resulted in cerebellar ataxia, hydrocephalus, and epilepsy. Multiple other organs have been reported to be affected by XD including the bone marrow, heart, lungs, kidney, stomach, jejunum, pancreas, uterus, musculature, and the hepatobiliary system. Three clinical patterns have been described in the literature: 1) spontaneously resolving 2) persistent cutaneous 3) progressive with systemic involvement. At the present time, our patient's clinical presentation is consistent with the persistent cutaneous form.

The pathogenesis of XD is not well understood and the majority of patients are normolipemic suggesting that this condition is unlikely to be related to a systemic disturbance in lipid metabolism or transport. The condition is thought to be driven by a secondary reactive proliferation of histiocytes and accumulation of lipid within the skin and various organ systems. Importantly, XD has reported associations with multiple myeloma, Waldenstrom's macroglobulinemia, and monoclonal gammopathy and laboratory evaluation for these condition should be considered.

Histopathologic features vary by the stage of the lesion but typically demonstrate a diffuse dermal infiltrate of foamy histiocytes, touton giant cells, and mixed inflammatory infiltrate consisting of lymphocytes, plasma cells, and neutrophils. Immunohistochemical studies when performed demonstrate histiocytes expressing CD68 and factor XIIIa and lacking expression of S100 and CD1a.

The differential for this condition includes juvenile xanthogranuloma, progressive nodular histiocytoma, generalized eruptive histiocytoma, multicentric reticulohistiocytosis, and eruptive xanthoma, but these can be distinguished from XD by various clinical and histopathological features.

XD is diagnosed primarily by clinical presentation combined with characteristic histopathology described above. Given the potential for multi-system involvement and association with blood dyscrasias, other diagnostic considerations include basic lab work including CBC, CMP, UA, lipid profile SPEP/UPEP/IFE and appropriate imaging guided by a full review of systems, especially upper airway symptoms and symptoms of diabetes insipidus such as polydipsia and polyuria. Appropriate sub-specialties should also be involved to assist with managing organ-specific sequelae of disease.

Treatments are separated into localized and systemic and these two modalities are often used in combination. Destruction of lesions has been reportedly achieved with surgery, localized radiation therapy, cryotherapy, electrosurgery and ablative lasers. Various systemic therapies have been reported in the literature with only partial success including both steroidal and non-steroidal immunosuppressants, lipid-lowering agents, antimalarials, and antineoplastic agents. Of note, there is one report of partial but clinically significant remission of cutaneous lesions with 54 sessions of NB-UVB over a course of six months. Varied success has been reported with the use of cyclophosphamide, azathioprine, and vinblastine chemotherapy either alone or in combination with prednisone. For our patient, the decision to utilize IVIg and currently, cladribine was made as noted above. We plan to reassess the patient after his third cycle of treatment with chemotherapy.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE 5**

Presented by Carrie Stull, MD, Warren Piette, MD, Faiyaaz Kalimullah, MD
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HISTORY OF PRESENT ILLNESS

A 61-year-old male presented for evaluation of a lesion on the right upper eyelid of three months duration. He denied associated pruritus or pain, and had applied hydrocortisone 1% ointment without improvement. Review of systems was negative for fevers, chills, night sweats, and unexplained weight loss. However, he reported an enlarged lesion on the left neck that had been present for approximately 20 years. The patient had been told by his primary care physician that the neck lesion was a cyst and did not require further work-up.

PAST MEDICAL HISTORY

Myasthenia gravis, anti-acetylcholine receptor antibody positive, s/p thymectomy, asthma psoriasis, hypertension, hyperlipidemia, gout

MEDICATIONS

Allopurinol
Atorvastatin
Famotidine
IVIg
Lisinopril
Montelukast
Mycophenolate mofetil
Prednisone
Terbutaline
Triamterene-hydrochlorothiazide

FAMILY HISTORY

Non-contributory

SOCIAL HISTORY

Non-smoker

PHYSICAL EXAM

Examination revealed a 1.5 x 1.5 cm eroded red plaque extending to the right upper eyelid margin. A 3 cm mobile subcutaneous nodule was palpable along the left neck.

PATHOLOGY

Right upper eyelid: Dense dermal infiltrate of atypical large and occasionally multinucleated cells extending to the epidermis. Immunohistochemical stains for CD30, CD15, PAX-5, CD79a and CD3 were positive while CD20, CK5, CK8/18, ALK and p63 were negative. Epstein-Barr encoding region in situ hybridization was negative.

Left neck: Schwannoma

Bone marrow biopsy: Aspirate smear and peripheral blood smear were normal

LABORATORY RESULTS
CBC with differential, CMP, LDH, HIV antigen and antibody, and EBV PCR were all within normal limits/negative.

IMAGING RESULTS
CT neck showed a subcutaneous nodule overlying the left sternocleidomastoid muscle.

CT chest abdomen and pelvis was normal.

PET scan showed hypermetabolic irregular thickening of the right eyelid and an enlarged hypermetabolic lesion on the left neck. Findings were otherwise unremarkable.

DIAGNOSIS
Cutaneous Hodgkin lymphoma in the setting of iatrogenic immunodeficiency

TREATMENT AND COURSE
The patient was referred to hematology/oncology and underwent a thorough staging work-up to assess for nodal and/or extranodal involvement. Imaging revealed an enlarged hypermetabolic lesion on the left neck. This raised concern for possible nodal involvement; however, the lesion was biopsied and found to be a schwannoma. Thus, no evidence of extracutaneous involvement was detected. Given reported associations between immunosuppression and development of Hodgkin lymphoma, mycophenolate mofetil was discontinued. The patient remains on IVIg and prednisone for treatment of myasthenia gravis and will be monitored closely. The patient is currently considering treatment options for Hodgkin lymphoma. Given the risk of progression to systemic involvement, he will likely receive multi-agent chemotherapy with or without local radiotherapy.

DISCUSSION
Hodgkin lymphoma (formerly known as Hodgkin's disease) is a predominantly B cell lymphoma that rarely affects the skin. The classic form of Hodgkin lymphoma (cHL) accounts for 90% of cases. Lymphadenopathy is detectable in the majority of patients at presentation and often involves cervical or supraclavicular nodes. B symptoms including fever, night sweats, and unexplained weight loss occur in less than half of patients and are more common in the setting of advanced disease. Generalized pruritus occurs in approximately 10-15% of patients and may precede the diagnosis of cHL by several months.

Diagnosis of cHL is achieved through histopathology demonstrating pathognomonic Hodgkin/Reed-Sternberg (HRS) cells admixed with a polymorphous inflammatory infiltrate. The immunophenotype of malignant cells characteristically includes expression of CD30, CD15, and PAX5. Expression of PAX5 helps distinguish cHL from other CD30 positive lymphoproliferative disorders including anaplastic large cell lymphoma, which may otherwise appear similar histologically. In fact, some cases of anaplastic large cell lymphoma were misdiagnosed as cHL prior to widespread use of immunohistochemistry.

Cutaneous involvement in cHL is rare, occurring in approximately 0.5% of cases. Presentation typically consists of papules or nodules distal to involved lymph nodes that arise from retrograde lymphatic spread. Noncontiguous spread and/or hematologic dissemination are uncommon but have been reported in the setting of immunodeficiency. Cutaneous involvement is generally thought to signify advanced disease and is associated with poor prognosis. Fewer than 15 reports in the literature have described primary cutaneous cHL without detectable nodal or

systemic involvement at the time of presentation. Many of these patients subsequently progressed to develop systemic disease.

The majority of cases of cHL arise in patients who are immunocompetent. However, development of cHL has been described in HIV+ individuals, solid organ transplant recipients and patients with autoimmune disease requiring immunosuppressive therapy. Our patient had received immunosuppressive therapy for at least 12 years prior to presentation for treatment of myasthenia gravis. Epstein-Barr virus (EBV) can be found in HRS cells in the majority of cHL cases associated with immunodeficiency. However, EBV was not detected in our case, and the significance of EBV in cHL pathogenesis is not well understood. Limited literature is available describing prognosis and treatment in cases of cHL arising in the setting of iatrogenic immunodeficiency. However, withdrawal of immunosuppressive agents is recommended when possible.

Treatment of cHL is selected based on disease stage and prognostic factors. Patients with early stage disease have a favorable prognosis and a high likelihood of achieving long-term complete remission. First-line treatment often consists of multi-agent chemotherapy involving doxorubicin, bleomycin, vinblastine, and dacarbazine. In addition, radiotherapy may be utilized in some cases. Additional treatments for refractory disease include autologous stem-cell transplantation and use of anti-PD1 antibodies.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE 6

Presented by Christina Foschi, BS, Katie Maloney, MD, Kyle Amber, MD
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HISTORY OF PRESENT ILLNESS

This patient is a 36-year-old female with a past medical history significant for Crohn's disease diagnosed in 2007, complicated by stricture and fistulas s/p colectomy with permanent end ileostomy, who originally presented to dermatology in January 2020 for an evaluation of fissures involving her labia majora, labia minora, and perianal region. At that time, her luminal Crohn's disease was well controlled on azathioprine and infliximab. Given the location and appearance of her cutaneous lesions, she was diagnosed with cutaneous Crohn's disease and started on a 2-3 month prednisone taper, which led to a complete resolution of her cutaneous activity within a few weeks. A few months later, she presented again with a flare of her cutaneous disease. She was no longer on infliximab due to loss of coverage by her insurance. High dose oral corticosteroids were restarted for multiple weeks with no improvement in her symptoms. Given that there was no appreciable clinical response, prednisone was substituted for cyclosporine, which led to only 40-50% improvement in her perianal ulceration. Cyclosporine was tapered and dapsone was added for additional control, but her non-healing wound remained. During this time, wound cultures for HSV and CMV were performed and were negative. Due to multiple therapeutic failures, she was started on monthly IVIg after a joint discussion between her dermatologist and gastroenterologist. Treatment was complicated by the development of symptomatic hypomagnesemia and an exacerbation of her cutaneous disease, so cyclosporine and dapsone were discontinued. At this point, an additional course of methylprednisolone was initiated, with no significant improvement after three weeks. Given the challenging presentation and unusual response of presumed cutaneous Crohn's disease, a four mm punch biopsy and tissue culture were performed from erythematous skin approximately one cm from the ulcer. Her pathology revealed dermal scar with chronic inflammation and tissue culture grew *Actinomyces turicensis*. Shortly after, she was admitted at an outside hospital for worsening pain and dehiscence of her perianal ulcer. MRI revealed a possible fistula extending from the wound to her posterior vaginal wall. Exam under anesthesia confirmed a fistulous tract extending to the base of the introitus; however, when dilute methylene blue was inserted into the vaginal vault, there was no evidence of any extravasation into the perineal wound. She was started on IV penicillin for a six week course, followed by two to four months of oral amoxicillin. At her most recent dermatologic follow-up, six weeks after starting antibiotics, she endorsed continued significant pain in the perianal region. Examination revealed a persistent knife-like longitudinal erosion with increased purulent drainage, overall appearing worse than prior.

PAST MEDICAL HISTORY

Crohn's Disease

PAST SURGICAL HISTORY

Colectomy 2019

MEDICATIONS

Tramadol
Dapsone 50mg QD
Magnesium Supplementation QD
IVIG 2g/kg monthly

ALLERGIES
Hydrocodone-Acetaminophen (pruritus)

FAMILY HISTORY
No pertinent family history

SOCIAL HISTORY
No tobacco or recreational drug use

PHYSICAL EXAM
Longitudinal knife-like erosion from superior gluteal cleft extending to perianal region with purulent drainage, sparing the vulva and perineum.

HISTOPATHOLOGY
Biopsy of the intergluteal fold on 2/9/2021 showed dermal scar and chronic inflammation with parakeratosis, mild epidermal hyperplasia, dermal scar and mild perivascular lymphoplasmacytic infiltrate. No granulomas or other changes suggesting active Crohn's disease were present. Cytopathic changes of herpes virus infection were not identified.

LABORATORY RESULTS
OSH (2020): HSV-1/2 not detected; EBV IgG positive, IgM negative; Magnesium 1.5; CMV negative; STD screening (Chlamydia, Gonorrhea) negative

Creatinine	1.15
Magnesium	1.8
Anaerobic Tissue Culture	Growth of *Actinomyces turicensis*

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

IMAGING
MRI: probable wound dehiscence with suspected fistulous tract extending to the posterior vaginal wall

DIAGNOSIS
Perianal ulcer with sinus tract and possible anovaginal fistula complicated by infection with *Actinomyces turicensis*

DISCUSSION
Perianal disease can be a severe and debilitating manifestation of Crohn's disease, occurring in up to 50-80% of individuals diagnosed with the disease. It manifests as skin tags, anal fissures, anal stenosis, perianal abscesses, fistulas, and hemorrhoids. In the majority of cases, patients presenting with perianal disease have already been diagnosed with inflammatory bowel disease due to their luminal involvement. However, in 5% of cases, perianal disease is the only presenting symptom. Fistulizing perianal involvement, in particular, tends to be a predictor of poor long-term outcomes. Pathogenesis of fistulizing Crohn's disease includes increased production of transforming growth factor beta, tumor necrosis factor, and interleukin-13, as well as upregulation of matrix metalloproteinases, which leads to tissue remodeling and fistula formation. While the pathology of Crohn's disease typically demonstrates noncaseating granulomas, only a third of cutaneous cases may show this feature on histopathology, so lack of these findings does not rule out the disease. Cases of perianal Crohn's disease require a complete assessment of potential fistula formation with MRI to determine the anatomy of the fistula tracts and to rule out abscess formation. Medical management is the treatment of choice as surgical interventions can be associated with high complication rates. This includes biologics,

such as TNF alpha inhibitors, with infliximab showing the most promising results for perianal Crohn's disease complicated by fistula formation. Antibiotics (metronidazole or ciprofloxacin), immunomodulators (Azathioprine or 6-mercaptopurine), calcineurin inhibitors (tacrolimus or cyclosporine), and hyperbaric oxygen are other potential therapies. Local injection of mesenchymal stem cells are in phase II and III clinical trials and have shown promise in fistula closure. Treatment can be difficult and require long term, multimodal therapy.

While diagnosis and management of cutaneous Crohn's disease can appear straightforward, it is important to be aware of a potential infection that can both mimic and complicate inflammatory bowel disease. *Actinomyces* are Gram positive, filamentous, anaerobic bacilli with 25 validated species to date. *A. turicensis* was first characterized in 1995 and has been isolated from the lower gastrointestinal tract, female genital tract, and skin below the waist. It is more commonly found in females, and often colonizes intrauterine devices without causing a symptomatic infection. Originally, *A. turicensis* was thought to have an insignificant role in human infection and represent a non-virulent strain. However, an investigation by Sabble et al (1999) of various actinomyces strains analyzed from a range of human infections found several cases of mono-bacterial *A. turicensis* infection, suggesting their clinical relevance. In this review, 28 anogenital infections grew actinomyces without other aerobe or anaerobe species. An additional review in 2010 by Chudackova et al found seven anogenital infections including abscesses, furuncles, carbuncles, and pilonidal cysts, where *A. turicensis* was isolated. Most notably, two of these cases lacked concomitant flora.

While a rare pathogen to isolate, successful identification of the *Actinomyces* species in a wound occurs only a fraction of the time due to high culture failure rates. The pathogen is difficult to grow in culture due to secondary polymicrobial infections, inadequate culture conditions, or insufficient short-term incubation. *Actinomyces* species remains a penicillin-sensitive group and, therefore, the mainstay of therapy is high dose penicillin for two to six weeks intravenously followed by oral antibiotics for 6 to 12 months. If treatment is inadequate, relapses can occur, which can contribute to significant morbidity due to the chronicity of the illness. Often, lesions resolve with antibiotics alone, but occasionally surgery may be needed as adjunctive therapy for complex lesions that have major anatomical fistulas or disruptions.

Actinomyces infection is indolent and can have nonspecific presenting symptoms such as pain, swelling, fevers, and weight loss. While a rare entity, there are reported cases in the literature of abdominal and anorectal primary *Actinomyces* infection mimicking inflammatory bowel disease through the formation of sinus tracts and fistulas. *A. Israelli* is the most commonly isolated pathogen. Additionally, there are also few case reports of abdominal actinomycosis occurring in the setting of Crohn's disease, although none of these cases involved *A. turicensis*. In anorectal actinomyces, treatment is often delayed due to failure of treating physicians to consider the diagnosis. The differential diagnosis typically includes inflammatory bowel disease, hidradenitis suppurativa, tuberculosis, malignancy, and sexually transmitted infections such as lymphogranuloma venereum. The underlying mechanism of infection is thought to be defects in the bowel wall from active Crohn's disease that allow the species to invade and establish sinus tract formation.

Given the fact that actinomyces infection and cutaneous Crohn's disease can both cause draining sinuses and fistula formation, our patient's presentation is challenging. While her case initially presented and responded in a way that is typical for cutaneous Crohn's disease, her subsequent recalcitrance to corticosteroids and failure to improve with multiple therapies led to the investigation of another possible underlying cause. Her wound grew an organism that has

been proven to be pathogenic in various anogenital and other types of infections, yet she failed to improve - and even worsened clinically - despite standard of care antibiotic therapy.
It is possible that her Crohn's disease initially did not improve due to her comorbid anorectal actinomycosis, and following initiation of treatment for her infection, her Crohn's disease continued to flare in the setting of discontinuation of biologic therapy and corticosteroids. It is also possible that in the setting of high dose oral corticosteroids, her infection worsened and given the extent of involvement, may be slow to respond to antibiotic therapy.

In conclusion, although the *Actinomyces* species is rare, it is an important pathogen to be aware of, particularly in persistent urogenital or anogenital disease that is refractory to standard treatment. We currently plan to continue treatment with amoxicillin and restart infliximab given her good clinical response to this medication in the past.

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