PROTOCOL BOOK • MAY 1, 2024

CHICAGO DERMATOLOGICAL SOCIETY

Monthly Meeting

Co-hosted by RUSH University Department of Dermatology

Chicago Dermatological Society

PROTOCOL BOOK
May 1, 2024

Co-hosted by
RUSH University Department of Dermatology

Guest Speaker: **M. Peter Marinkovich, MD**
Stanford University School of Medicine

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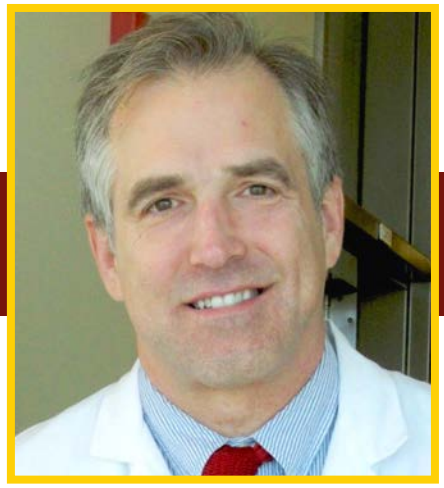
INVITED GUEST LECTURER

M. Peter Marinkovich, MD



Dr. Marinkovich completed research/residency training in Portland Oregon under Dr. Robert Burgeson, assisting in the discovery of type VII collagen and laminin-332 and elucidating the molecular defects of dystrophic and junctional epidermolysis bullosa. After joining the faculty at Stanford University School of Medicine, his group has focused on basement membrane biology and gene transfer methodology, most recently bringing three dystrophic epidermolysis bullosa gene therapy programs from preclinical to phase 3 levels. Last year, one of his therapies, a topical HSV-1 based corrective therapy for epidermolysis bullosa called Beremagene Geperpevec, became the first FDA approved gene therapy in dermatology. Dr. Marinkovich directs the bullous disease clinic at Stanford and is a clinical expert on both autoimmune and inherited bullous diseases.

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PROGRAM

Co-hosted by
RUSH University Department of Dermatology

May 1, 2024
University of Chicago Gleacher Center

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors**
8:30 a.m. - 10:15 a.m.	**Clinical Rounds** Slide viewing/posters – ongoing through the early morning
9:00 a.m.	**Welcome and Opening Comments** *Morayo Adisa, MD - CDS President*
9:00 a.m. - 10:00 a.m.	**Morning Lecture: Gene Therapy for Epidermolysis Bullosa** *M. Peter Marinkovich, MD*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:00 p.m.	**Resident Case Presentations & Discussion**
12:00 p.m. - 12:30 p.m.	**Box Lunches & Visit with Exhibitors**
12:30 p.m. - 1:00 p.m.	**CDS Business Meeting**
1:00 p.m. - 2:00 p.m.	**Afternoon Lecture: Epidermolysis Bullosa: Clinical and Pathophysiologic Features** *M. Peter Marinkovich, MD*
2:00 p.m.	*Program adjourns*

RUSH UNIVERSITY

RUSH University Department of Dermatology

Chicago Dermatological Society Meeting
May 1, 2024

Dermatology Residents

Fourth Year
Julie de la Cruz
Morgan Decker

Third Year
Elise Brunsgaard
Rachel Lefferdink
Emily Medhus

Second Year
Alexandra Eckburg
Maria Mihailescu
Alex Rokni

TABLE OF CONTENTS

Resident Case Presentations & Discussion

CHICAGO DERMATOLOGICAL SOCIETY
Treatment Considerations in Pemphigus Vulgaris; Approaches to Achieving Durable Remission

CASE #1

Presented by Alex Rokni, MD, Kyle Amber, MD
Department of Dermatology, RUSH University Medical Center

CASE 1A

HISTORY OF PRESENT ILLNESS

A 23-year-old female with no significant past medical history presented to dermatology clinic with several weeks of diffuse painful, crusty and desquamating plaques, eye pain and dryness, as well as chills and decreased oral intake. She was initially seen at an outside dermatology office and diagnosed with pemphigus vulgaris via punch biopsy 4 months prior. Current treatment consisted of prednisone 10mg and triamcinolone ointment.

PAST MEDICAL & SURGICAL HISTORY

Hypertension

FAMILY HISTORY

No known family history of autoimmune skin disease.

SOCIAL HISTORY

No pertinent history.

MEDICATIONS

Prednisone 10mg daily
Triamcinolone 0.1% ointment

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Febrile to 100.1, Tachycardic to 104
Face and scalp with erosions and thick yellow keratotic crusting and periocular involvement. Lips with hemorrhagic crusting. Trunk and extremities with scattered erosions and yellow and hemorrhagic crusting. Extensive full thickness epidermal sloughing on back with positive Nikolsky sign.

LABORATORY RESULTS

Abnormal Results
CBC with elevated neutrophils (78.3%)
Immunoserologic Pemphigus Panel:
Indirect Immunofluorescence Cell Surface IgG Antibodies:
+ 1:2560 (H), monkey esophagus
+ 1:5120 (H), intact human skin

ELISA Desmoglein 1 & 3 IgG Antibodies:
IgG Desmoglein 1 antibodies: 1528 units (H)
IgG Desmoglein 3 antibodies: 846 units (H)

Normal Results
CMP, Blood cultures

IMAGING STUDIES
None

DERMATOPATHOLOGY
Outside pathology report reviewed: Direct Immunofluorescence showing IgG reactive granular deposits at the intercellular spaces in the epidermis.

DIAGNOSIS
Pemphigus Vulgaris (PV)

CLINICAL COURSE
The patient was directly admitted for treatment of extensive PV due to risk of fluid imbalance as well as concern for superimposed bacterial and high likelihood of HSV infection. She was initially stabilized on high dose IV steroids (125 mg methylprednisolone) and started on a combined treatment of Rituximab (RTX) and Intravenous Immunoglobulin (IVIG) according to the Ahmed et al. protocol.[1] Additional treatment included doxycycline 100 mg BID, therapeutic valacyclovir dosing 1 g TID with plan to taper to prophylactic dosing (500 mg daily) after one week. Osteoporosis prophylaxis was also started given plan for long term high dose steroids. Vegetative skin plaques were treated topically with gentle mineral oil debridement. She received her first RTX infusion the following day and was discharged 1 day later on 96 mg PO methylprednisolone daily (including the additional treatments listed above) with a plan for follow up in clinic in one week.

After one week, most of the lesions on the patient's face, trunk, and extremities had crusted over and dried up. The following infusion schedule was continued: during weeks 1-3 the patient was given RTX (375 mg/m^2) once a week for 3 weeks and then week 4 she was given IVIG (2 g/kg), divided over 2 days. Steroids were tapered every 3 weeks at approximately 25-33%. After 7 weeks on treatment, there was dramatic improvement with no PV activity: the patient's face was nearly clear with minimal post-inflammatory erythema and all lesions on the trunk and extremities had healed with focal post-inflammatory hyperpigmentation. The treatment protocol described below was followed with oral steroids tapered off over 7 months total. The full treatment regimen was completed over 3 years and the patient is now in remission almost 4 years from treatment initiation.

Treatment protocol
Rituximab Q6 months
- Month 1 - 2: 375 mg/m^2 weekly x 3 weeks
- Month 3 - 6: 375 mg/m^2 once monthly
- Month 6 - 24: 375 mg/m^2 every 6 months

IVIG:

- 2 g/kg Monthly (divided over 4 days) continued for 6 months from the time of complete response off of steroids
- 2 g/kg (divided over 4 days) every other month for 6 months
- 2 g/kg (divided over 4 days) every 3 months over 6 months

Oral Steroids tapered every 3 weeks until off at 25-33% (accelerated slightly 3 - 4 months into treatments)
Therapy was discontinued after 6 months of Q3-month IVIG.

CASE 1B

HISTORY OF PRESENT ILLNESS

A 72-year-old man with a longstanding history of pemphigus vulgaris (>30 years) presented with worsening redness of a chronic lesion on his right nasal sidewall. The lesion was not responding to topical steroid treatment. Current systemic treatment consisted of azathioprine and chronic low dose prednisone, unable to taper off.

PAST MEDICAL & SURGICAL HISTORY

Hypertension

FAMILY HISTORY

No known family history of autoimmune skin disease.

SOCIAL HISTORY

No pertinent history.

MEDICATIONS

Prednisone 5 mg, alternating with 2.5 mg daily (prior flared with attempted tapers)
Azathioprine 125 mg daily (75 mg QAM, 50 mg QPM)
Topical fluocinonide 0.05% cream daily PRN

ALLERGIES

NKDA

PHYSICAL EXAMINATION

Right nasal ala with well circumscribed erythematous plaque. No oral mucosal lesions. Scattered hyperpigmented macules on the face and scalp. Nikolsky sign negative.

LABORATORY RESULTS

CBC and CMP within normal limits

IMAGING STUDIES

None

DERMATOPATHOLOGY

None

DIAGNOSIS
Pemphigus Vulgaris

CLINICAL COURSE
Given stable remission for several years on low dose prednisone (5 mg and 2.5 mg alternating daily) and azathioprine, a slow steroid taper was attempted. Prednisone dose was decreased to 2.5 mg daily for 3 months without disease activity. Upon decreasing prednisone by 0.5 mg (to 2.0 mg daily) patient experienced several painful oral erosions and worsening erythema and tenderness of his chronic nasal sidewall lesion. Prednisone dose was increased to 5 mg daily which resolved the oral lesions over several weeks. However, the nasal lesion persisted. Tacrolimus ointment twice daily did not yield any improvement. Two injections of intralesional triamcinolone (2 mg/cc x 1 cc) spaced over 2 months showed minimal efficacy. Intralesional RTX (10 mg/cc x 0.5 cc) was attempted with notable improvement in the nasal lesion after one injection. Four months later the patient received two additional rounds of intralesional RTX (at the same concentration) spaced by 1 month. The nasal ala plaque was asymptomatic with continued decreasing faint erythema over the course of the injections and the patient was very satisfied with the improvement. The patient continues to be slowly tapered off of steroids.

DISCUSSION
Initial treatment of PV is typically with high dose corticosteroids. However, to minimize the effects of long-term steroid use and achieve remission, most patients will require one or more steroid-sparing agent. RTX is widely considered a mainstay of treatment in severe PV. However, not all dosing regimens have the same response rates or relapse rates. For instance, the lymphoma dosing regimen (RTX 375 mg/m^2 weekly for 4 weeks) is associated with significantly higher rates of achieving remission when compared to the rheumatoid arthritis dosing regimen (1000 mg infusions 14 days apart).[2] Furthermore, in a meta-analysis of 155 patients comparing such protocols, more weeks of RTX loading doses showed significantly longer time to relapse.[3]

In terms of overall relapse rates in PV on RTX monotherapy, one retrospective cohort study of 112 patients (who received between 2-5 doses on various dosing protocols) showed 50% of patients relapsed within almost 2 years (23.3 months) and roughly 80% relapsed after 4 years of achieving complete remission off therapy.[2]

Scheduled maintenance RTX infusions may help to decrease these relapse rates in such patients. Rashid et al. analyzed the effectiveness of rituximab with and without maintenance infusions. Retrospective data was obtained from patients with pemphigus vulgaris and pemphigus foliaceus treated with rituximab over a 5-year period. Patients were given routine maintenance regardless of whether they achieved complete remission or not. Relapse rates were analyzed as during the first 3 years after initial rituximab infusion. Those who received maintenance RTX infusions at 6 and 12 months from treatment initiation had significantly lower rates of relapse (40% vs 71%).[4] Notably, this was despite these patients having more severe disease, which is evidenced by relatively high corticosteroid dosing in the study patients. Nevertheless, overall relapse rates still approached 40-71% regardless of RTX maintenance dosing.[4]

Therefore, to prevent relapse and ensure durable remission, an alternative approach to therapy is to utilize more intensive protocols combining RTX with or without additional IVIG. The first of such protocols was reviewed by Ahmed et al. Patients received two cycles of RTX (375 mg/m^2) once weekly for 3 weeks and IVIG (2 g/kg) in the fourth week, followed by monthly infusions of RTX and IVIG for 4 consecutive months. The initial study of 11 patients with PV showed clinical remission lasting on average 31.1 months (ranging from 22-37 months) in all but 2 patients.[1] A subsequent study following 10 of their initial 11 patients over 10 years from discontinuation of RTX demonstrated that all patients maintained durable remission off all therapy.[5]

It is important to note that in the initial Ahmed et al. protocol, patients were given seven additional infusions of IVIG if they were clinically free of disease after the first 6 months of aggressive therapy. Yet the lack of a standardized stop time for the protocol makes application in clinical practice challenging. An alternative protocol by Grando mirrors the Ahmed et al. protocol of combined RTX and IVIG however provides a more standardized means of tapering IVIG and discontinuing all therapy. It also adds concomitant tetracycline and niacinamide therapy to the treatment regimen which adds synergistic protection to keratinocytes. In this protocol 100% of patients achieved long term remission off therapy.[6] Furthermore, this study showed very low relapse rate while on treatment (8.7%) and after completion of the treatment protocol (4.3%). Comparing these rates to literature reports approaching 80% relapse rates after RTX protocols without IVIg, there is an apparent benefit to adding IVIG to Rituximab in order to achieve durable remission off therapy.[6]

Thus, when choosing a treatment regimen for patients with PV, increased dosing and regular maintenance therapy of RTX can improve both the time to and durability of response. In addition, retrospective studies demonstrate that concomitant IVIG may increase response rates and improve long term remission off therapy. In our case 1a, therapy as described above with RTX and IVIG induction and maintenance dosing over a 3-year period was chosen in order to give this relatively young and otherwise healthy patient with a severe PV presentation the best odds of remission. As the addition of IVIG treatment comes at significant time burden and cost, the aforementioned statistics should be considered on an individual basis with patients to determine the best possible treatment protocol.

In case 1b, we describe the course of a patient with longstanding PV who has achieved partial response, with a solitary chronic lesion. Therapies for chronic PV lesions in the absence of other systemic disease manifestations range from topical and intralesional to systemic therapies as described above. In order to choose the most effective and precise therapy in this case, it is important to consider how chronic PV lesions may behave differently from systemic PV.

Studies have evaluated the role of infiltrating immune cells in lesional skin and shown that in chronic PV lesions, there are collections of B-cells and T-cells which can form pseudo-lymphoid aggregates.[7] Furthermore, many of these B-cells appear to be antigen specific, leading to in situ B-cell differentiation and clonal expansion within ectopic lymphoid-like structures.[8] Based on this principle, intralesional therapy may be preferred in cases of few, isolated chronic PV lesions. Several case reports and case series have shown improvement of refractory PV lesions with intralesional rituximab (ILR).[9, 10] In addition, one study of 11 patients with refractory PV lesions

showed that after ILR, not only did the average number and size of lesions decrease, but there was also a significant decrease of circulating CD19+ B lymphocytes.[11]

Studies have also aimed to compare ILR with the much cheaper and more widely available intralesional triamcinolone (ILT). In one study of 21 patients with refractory PV lesions treated with either ILT or ILR, both therapies were effective in decreasing the size of these lesions. However, the study failed to demonstrate a significant difference between the effectiveness of ILT vs. ILR.[12] Yet given the small sample size, this may have been underpowered to identify a statistically significant difference in efficacy between the two therapies.

Thus, given our case 1b and the relatively new and limited literature on treatment of chronic recalcitrant PV lesions with ILR, in the absence of further diffuse involvement of PV, ILR may be beneficial as a second line agent to ILT.

KEY POINTS

- In systemic management of severe PV, alternative protocols exist which may optimize response and relapse rates. These may be discordant with current FDA approved protocols which were chosen to match other rheumatologic indications rather than for specific scientific rationale.
- Combined use of RTX and IVIG may improve durable remission but this should be weighed with the additional time and cost of IVIG therapy.
- For chronic, recalcitrant PV lesions in the absence of further diffuse involvement, intralesional RTX may be beneficial as a second line agent to intralesional triamcinolone.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE #2

Presented by Julie de la Cruz, MD, Maureen Riegert, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 43-year-old female presented to our dermatology clinic for an eight-year history of a rash on her right cheek that started around the time of delivery of her son, which she was self-treating with charcoal soap, with no improvement. At this initial visit her rash was felt to be consistent with a combination of acne vulgaris, acne scarring, post inflammatory hyperpigmentation and she was started on doxycycline 100 mg twice daily, an over-the-counter benzoyl peroxide cleanser to use once daily, and a compounded topical hydroquinone/kojic acid/tretinoin lightening cream for nightly use. The patient was recommended to follow up in three months, however did not return to clinic until one year later. When she returned for evaluation one year later, there was significant worsening of her rash, now involving her entire face. On physical exam, she was noted to have numerous erythematous to violaceous pustules and papulonodules coalescing into plaques involving the forehead, cheeks, nose, and chin, with marked facial edema that was more pronounced on the right side of the face.

PAST MEDICAL & SURGICAL HISTORY

Morbid obesity (BMI 59.25), obstructive sleep apnea

FAMILY HISTORY

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

SOCIAL HISTORY

No history of smoking, drinks wine rarely, no recreational drug use.

MEDICATIONS

None

ALLERGIES

None

PHYSICAL EXAMINATION

Numerous erythematous to violaceous pustules and papulonodules coalescing into plaques involving the forehead, cheeks, nose, and chin, with marked facial edema that was more pronounced on the right side of the face. No comedones were appreciated on exam.

LABORATORY RESULTS

CBC with differential- normal
CMP- normal
Lipid panel- normal
Urine pregnancy test- negative

IMAGING STUDIES
None

PATHOLOGY
Histopathologic analysis of the 4mm punch biopsy showed dilated follicular infundibula containing neutrophils and surrounding acute and chronic inflammation. Gram stain highlighted gram-positive cocci within inflamed follicles. PAS and GMS stains were negative for fungal forms.

DIAGNOSIS
Pyoderma Faciale (Rosacea Fulminans)

CLINICAL COURSE
After presenting with the fulminant onset of facial edema and erythematous to violaceous papulonodules, the patient underwent a 4mm punch biopsy and was started on a 4-week course of prednisone and a combined estrogen/progesterone oral contraceptive pill while initiating the approval process for isotretinoin. Labs were checked prior to initiation of isotretinoin, namely a CBC, CMP, lipid panel and urine pregnancy test, which were all unremarkable. Her biopsy results showed a suppurative folliculitis, and when combined with the clinical picture, supported the diagnosis of pyoderma faciale.

After one month, the patient was started on low dose isotretinoin at 10mg daily and her prednisone was slowly tapered over the next month. The patient showed marked improvement on this regimen and after a month, her isotretinoin was further increased to 30mg daily. The patient's treatment is ongoing and she continues to show steady improvement.

DISCUSSION
Pyoderma faciale, also known as rosacea fulminans, is a rare cutaneous disorder characterized by the acute onset eruption of erythematous pustules, nodules, and draining sinuses with background facial erythema and edema. Pyoderma faciale was first described by O'Leary and Kierland in 1940 and was thought to be a variant of acne.[1] In 1992, Plewig and his colleagues reclassified pyoderma faciale as a severe variant of rosacea and suggested renaming the condition rosacea fulminans.[2]

The diagnosis of pyoderma faciale is mostly clinical, however, a thorough workup including a detailed medical history, physical examination, laboratory testing, and skin biopsy, is key. The differential diagnosis of pyoderma faciale includes but is not limited to acne fulminans, acne conglobata, acute cutaneous lupus erythematosus, gram negative folliculitis, abrupt onset acne in the setting of underlying ovarian tumor, facial Sweet's syndrome, as well as fungal and mycobacterial infections. Acne fulminans is perhaps the main differential for pyoderma faciale and has some distinct differentiating features that are important to be aware of. Pyoderma faciale typically affects women between the ages of 20-40, is confined to the face and neck, and has no comedones. Acne fulminans however generally affects adolescent males with a history of acne, has a more extensive distribution often involving the face, neck and trunk, and generally has more systemic symptoms including fever, arthralgias, and myalgias.[3]

The pathogenesis of pyoderma faciale is not completely understood but thought to be multifactorial due to a combination of immunologic, hormonal, and vascular factors. The upregulation of cathelicidin, kallikrein 5 and interleukin-8 is well documented in the pathogenesis of papulopustular rosacea and has been implicated in the pathogenesis in pyoderma faciale as well.[4] Cathelicidin is a major antimicrobial peptide found in human keratinocytes and plays an important role in the innate immune response by interacting with kallikrein 5 to regulate inflammation, reactive oxygen species formation, angiogenesis and protease function.[5,6] Meanwhile, interleukin-8 plays a role in neutrophil chemotaxis which plays a role in the formation of inflammatory lesions of rosacea and its variants.[4] Hormones are thought to play a large role in the development of pyoderma faciale given the predominance in women and multiple reports in pregnancy.[7-11] There have also been reports of diet and stress triggering rosacea fulminans.[12] Specifically, high dose vitamin B6 and B12 supplementation, and acute emotional stress, such as the loss of a loved one have been reported as triggers.[12,13] Furthermore, pyoderma faciale has been associated with multiple underlying conditions such as inflammatory bowel disease, particularly ulcerative colitis however there are also few reports of cooccurrence with Crohn's, hypothyroidism, and hepatic disease.[2,13,14,15]

Management of pyoderma faciale is typically comprised of systemic corticosteroid monotherapy for a few weeks followed by or in combination with low dose isotretinoin.[16] Although the combination of steroids and isotretinoin appears to be the standard of care for this condition, there may be obstacles to utilizing this combination, namely, insurance coverage and pregnancy. At present, isotretinoin is not FDA approved for the treatment of pyoderma faciale. Therefore, many insurance companies may deny coverage, making it more difficult for patients to obtain the medication. Secondly, the association between pregnancy and pyoderma faciale is well documented, and therefore isotretinoin is not an option for this patient population. Thankfully, multiple different treatment options exist and have been reported with varying levels of success. Previous authors have published on treating pyoderma faciale with different topical medications such as corticosteroids, permethrin, metronidazole, and ivermectin. Many different systemic medications have also been used to successfully treat pyoderma faciale such as doxycycline, minocycline, tetracycline, azithromycin, trimethoprim-sulfamethoxazole, and dapsone.[3,7,9,16,17] Overall, management requires prompt intervention and close monitoring to prevent disfiguring scarring. The management plan should be based on patient's response to treatment and adjusted as needed.

KEY POINTS

- Keep Pyoderma Faciale in mind for abrupt onset edematous facial papulonodules
- Start treatment early to prevent scarring
- Treatment depends on extent of involvement however typically with a combination of steroids and isotretinoin

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CHICAGO DERMATOLOGICAL SOCIETY **CASE #3**

Presented by Morgan E. Decker, MD, MS, Olga Gomeniouk, BS, David C. Reid, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 67-year-old woman was transferred to our institution for further work-up and surgical repair of an ascending aortic dissection. She had been admitted to an outside hospital after an outpatient echocardiogram and subsequent CT angiogram of the chest, abdomen, and pelvis showed possible aortic dissection. One week prior to transfer, she also developed painful oral ulcers on the left lateral tongue. She had no prior history of oral or genital ulcers and denied constitutional symptoms. The patient endorsed engaging in unprotected oral and vaginal sex with one male partner. She had no known history of sexually transmitted infections.

Two days after the onset of oral ulcers, the patient developed a lesion on her right dorsal hand overlying the fifth metacarpophalangeal joint. She reported the skin was normal prior to onset and denied inciting trauma. She stated that the lesion was tender and enlarging. The patient was noted to have an acute kidney injury on chronic kidney disease and anemia on admission.

PAST MEDICAL & SURGICAL HISTORY

Coronary artery disease status post five coronary artery bypass grafts, atrial fibrillation/sick sinus syndrome status post permanent pacemaker implantation, peripheral artery disease, chronic kidney disease, hypertension, hyperlipidemia, hypothyroidism, and tobacco use disorder

MEDICATIONS

Atorvastatin, alendronate, aspirin, hydralazine, levothyroxine, metoprolol

REVIEW OF SYSTEMS

Negative for fevers, chills, sweats, fatigue, cough, nausea, and vomiting

PHYSICAL EXAMINATION

Left lateral tongue: large yellowish, firm nodule with central ulceration
Right fifth metacarpal joint: overlying firm, violaceous, flat-topped, hemorrhagic plaque

LABORATORY RESULTS

CBC with differential: normocytic anemia (Hgb 7.9, MCV 85.4, RDW 17.5) and thrombocytopenia (PC 129)

CMP: azotemia (serum creatinine 2.88, BUN 38), hypoproteinemia (total protein 5.7) with hypoalbuminemia (1.7), and hypocalcemia (8.5)

Infectious work-up: positive RPR (1:1) and treponemal confirmatory test (reactive FTA-Abs). Negative HSV-1 & HSV-2 PCR, HIV antigen/antibody, and urine gonococcal/chlamydia

Autoimmune work-up: positive ANA (1:1,280), c-ANCA (>1:640), anti-histone antibodies (6), RF (31), and anti-CCP antibodies (>250)

IMAGING STUDIES

CT angiogram of chest, abdomen, pelvis: Stable 6.5 x 7 cm ascending thoracic aorta aneurysm with acute aortic dissection, Stanford A/Debakey type II

PATHOLOGY

Punch biopsy, right dorsal hand (H&E) – Hyperplastic epidermis with vesicle formation and dense dermal neutrophilic infiltrate. Cryptococcus-like artifacts in the dermis. No interface change or vasculitis. PAS, GMS, and spirochete stains negative for fungal and treponemal organisms

Punch biopsy, right dorsal hand (DIF) – No specific immunodeposits detected with antibodies against IgG, IgA, IgM, C3, C1q, and fibrin

Needle biopsy, kidney – pauci-immune necrotizing and crescentic glomerulonephritis and acute tubular injury (ATN)

DIAGNOSIS

Iododerma secondary to iodinated contrast administered in the setting of hydralazine-induced c-ANCA vasculitis causing acute renal failure

CLINICAL COURSE

The patient was evaluated by cardiothoracic surgery, who recommended medical management of the ascending aortic dissection with nifedipine and carvedilol and close outpatient follow-up. Hydralazine was discontinued and the patient's renal function improved with temporary continuous renal replacement therapy, high dose steroids, and rituximab infusions every two weeks. Three weekly doses of IV penicillin G 2.4 million units were administered to treat the late latent syphilis. The patient's oral ulcers and hand lesion gradually improved throughout her admission.

DISCUSSION

Iododerma is a rare neutrophilic dermatosis that typically presents one to three days following exposure to iodine-containing substances such as oral potassium iodide supplements, amiodarone, topical povidone-iodine, and, most frequently, intravenous iodinated contrast material.[1] Although iododerma typically occurs in patients with renal dysfunction following iodine exposure due to reduced clearance of the substance, there have been reports of cases in patients with normal renal function.[2]

Iododerma classically affects sebaceous areas, but there are reports of lesions involving the trunk, extremities, and oral cavity, as seen in our patient.[3] Most commonly, iododerma presents as an acneiform eruption or as vegetative nodules; however, hemorrhagic bullae and plaques have also been described clinical manifestations.[1] In the setting of acute iododerma, histopathologic findings are nonspecific but may include a polymorphonuclear cell infiltrate with few eosinophils, mast cells, and plasma cells.[4] More recently, haloed cryptococcus-like structures, thought to represent degenerating histiocytes, were described histological features present in several cases of iododerma.[5,6] In our case, histopathology revealed a dermal neutrophilic infiltrate with prominent acellular bodies surrounded by capsule-like vacuolated spaces mimicking *Cryptococcus*. While characteristic histopathology and blood or urine iodine

levels may support a diagnosis of iododerma, it is largely a diagnosis of exclusion and treatment is supportive in nature. Skin lesions resolve in four to six weeks, occasionally leaving dyspigmentation in their wake.

Interestingly, several reports of iododerma have described patients with renal insufficiency who received iodinated contrast media with concurrent use of hydralazine.[6,7] In our case, the patient developed mucocutaneous lesions of iododerma after receiving iodinated contrast media in the setting of concomitant c-ANCA vasculitis complicated by pauci-immune glomerulonephritis that was presumed to be secondary to hydralazine. While this connection needs further elucidation, patients with impaired renal function taking hydralazine may have an increased risk of iodine toxicity following administration of iodinated contrast media.

KEY POINTS

- Iododerma is a rare manifestation of iodine toxicity that may be polymorphous in its clinical presentation.
- Histopathology of iododerma characteristically shows a dermal neutrophilic infiltrate with haloed structures mimicking *Cryptococcus.*
- Diagnosis of iododerma is one of exclusion but may be supported by dermatopathology and blood or urine iodine levels.
- Concurrent use of iodinated contrast media and hydralazine may confer an increased risk of iodine toxicity in patients with renal insufficiency.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE #4

Elise K. Brunsgaard, MD, Marie D. Lafeir, MD, Warren W. Piette, MD
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HISTORY OF PRESENT ILLNESS

The patient is a 69-year-old male presenting for an eight-month history of enlarging pink to red plaques involving his left arm and right thigh. He denied any systemic symptoms. A year and a half prior to presentation, the patient had a pink plaque on his left upper extremity which was biopsied and read as consistent with cutaneous lymphoid hyperplasia. It resolved following biopsy and treatment with clobetasol 0.05% ointment. He endorsed a prior history of atopic dermatitis which had been controlled on dupilumab for the past three years. Additionally, he had been diagnosed with ankylosing spondylitis and started on adalimumab two months prior to presentation.

PAST MEDICAL & SURGICAL HISTORY

Ankylosing spondylitis
Atopic dermatitis
Hypertension
Hyperlipidemia

FAMILY HISTORY

No history of lymphoma or lymphoproliferative disorders.

SOCIAL HISTORY

No tobacco or drug use.

MEDICATIONS

Atorvastatin, adalimumab, dupilumab, hydrochlorothiazide, irbesartan, nifedipine

ALLERGIES

None

PHYSICAL EXAMINATION

2x2 cm pink to red firm, non-tender nodule of left medial arm.
5.5x3 cm annular firm pink to violaceous plaque with central clearance of right lateral thigh.

LABORATORY RESULTS

CBC and CMP were within normal limits.

Initial blood flow cytometry showed two abnormalities. The first was the finding that 4% of the T cells showed a loss of CD7 and nearly all were CD4 positive, suggestive of blood involvement. The second was the presence of kappa restricted CD19 positive and CD5 positive B cells in 25% of the lymphocytes, concerning for an early coexisting chronic lymphocytic leukemia (CLL). However, repeat flow cytometry three months later showed no diagnostic abnormalities.

IMAGING AND DIAGNOSTIC STUDIES
PET-CT consistent with primary cutaneous disease.

DERMATOPATHOLOGY
A 4mm punch biopsy of the left medial arm plaque showed an atypical lymphoid infiltrate with a dense dermal infiltrate of medium sized lymphoid cells with an admixture of small mature lymphocytes. No epidermotropism, significant apoptosis or mitotic activity.

Immunohistochemical stains showed CD3/CD4 positive T cells with a CD4/CD8 ratio of approximately 4:1. T cells retained expression of CD2 and CD5. Some decrease in the expression of CD7 was seen and CD30 was essentially negative. T cells expressed Bcl-2 but were negative for Bcl-6. CD20 highlighted B cells in the background.

A shave biopsy of the right lateral thigh plaque showed dense and lymphoid cell infiltrate involving the reticular dermis. No evidence of epidermotropism, nodularity or germinal center formation. It was composed predominantly of medium sized pleomorphic lymphocytes with irregular nuclear contour and chromatin distribution with abundant clear cytoplasm. Scattered mitoses were also noted.

Immunohistochemistry showed the infiltrate was composed of primarily T cells (CD3 positive) with a significant component of B cells (CD20 positive) and a T/B cell ratio of approximately 3:1. The CD4/CD8 ratio was approximately 8:1. CD2, CD5 and CD7 appeared retained. CD30 was negative. Tumor cells were positive for BF1, CD5, ICOS (CD278) and PD1 (CD279) and negative for FOXP3. Ki67 (MIB-1/proliferative marker) showed proliferative activity within approximately 20% of the lesion.

T cell receptor beta gene rearrangement assay was performed and was positive for T cell clonality.

DIAGNOSIS
Primary cutaneous small/medium CD4+ lymphoproliferative disorder (PCSM-TCLPD)

CLINICAL COURSE
Both plaques partially regressed following biopsy and residual areas were treated with clobetasol 0.05% ointment twice daily until resolution. Dupilumab was held. He continues to be monitored by dermatology and hematology for recurrence or progression given multifocal presentation, initial positivity in the flow cytometry, and finding on initial flow cytometry concerning for early CLL.

DISCUSSION
PCSM-TCLPD is a rare, indolent disorder of T cells that was reclassified in 2016 by the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) from a lymphoma to a lymphoproliferative disorder based on unknown malignancy potential.[1,2] Typical clinical presentation is a solitary pink to red papule, plaque, or nodule on the head, neck, or upper trunk.[3–12] Multifocal plaques or nodules are rare.[8,13] Lesions are often

asymptomatic but can have associated pruritus. Usually seen in older adults, but rare pediatric cases have been reported.[14] Histology is characterized by a dense dermal infiltrate with small to medium CD4-positive T cells. Epidermotropism is rarely seen. The T cells exhibit a follicular helper T-cell phenotype including positivity of B-cell lymphoma 6 (Bcl-6), C-X-C motif chemokine ligand 13 (CXCL13), inducible co-stimulator (ICOS), and programed death 1 (PD-1).[15,16] PD-1 is most often expressed and Bcl-6 expression is variable. CD30 is typically negative, and the majority of cases have a low Ki67 index. T-cell receptor gene rearrangement shows clonality in around 60-100% of cases.[3,8,17] Differential diagnosis for PCSM-TCLPD includes cutaneous lymphoid hyperplasia, tumor stage of mycosis fungoides, cutaneous B-cell lymphoma, peripheral T-cell lymphoma, follicular T-cell lymphoma, and angioimmunoblastic T-cell lymphoma. If mucin is present on histopathology, Jessner lymphocytic infiltrate, tumid lupus, and reticular erythematous mucinosis may also be considered.[11]

There is no standard follow-up interval or treatment for PCSM-TCLPD. While many cases spontaneously resolve following initial biopsy, additional treatment options include high-potency topical corticosteroids, intralesional steroids, surgical excision, and localized radiation therapy.[2,3,7,13,18] Single cases have described success with phototherapy,[3] intralesional interleukin-2 combined with topical steroids,[19] and pulsed dye laser.[3] Local and distant cutaneous recurrence is rare, but treatment of recurrence involves the same skin direct therapies.[2,13] Given typically indolent course, prognosis for PCSM-TCLPD is excellent. For patients with the typical presentation of a solitary nodule or plaque, the estimated 5-year survival is 100%.[2,18] Prior to WHO-EORTC reclassification, overall survival was reported between 60 to 90% due to previous misclassification of more aggressive phenotypes including peripheral and follicular T-cell lymphomas.[5,6,18] Based on the excellent prognosis and indolent course, no further staging work-up is typically recommended.[2] There is limited data on prognosis of multifocal disease since the reclassification due to rare presentation, but it is thought to have more aggressive potential and closer monitoring is recommended.[4,6]

KEY POINTS

- Small/medium CD4+ lymphoproliferative disorder is a rare, indolent T cell disorder that was reclassified from a lymphoma to a lymphoproliferative disorder in 2016.
- Localized, skin-directed therapies are standard treatment.
- Previous variability in survival data was due to inclusion of more aggressive phenotypes prior to reclassification.
- Systemic work-up should be considered in multifocal disease.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE #5

Presented by Maria Mihailescu, MD and Parul Goyal, MD
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HISTORY OF PRESENT ILLNESS

A healthy 15-year-old girl was referred to our dermatology clinic for a 3 month history of a non-healing wound of the face. She described the onset of a pimple near her right lateral eyebrow which drained, ulcerated, and expanded over three months. She denied a history of trauma to the site, recent travel, outdoor exposure, or exposure to animals. She had been evaluated and treated by her primary care physician and in multiple emergency departments without success. She had failed to improve with various topical therapies and multiple courses of oral cephalexin, clindamycin, and doxycycline. She denied fevers, headaches, chills, weight loss, or flu-like symptoms.

PAST MEDICAL & SURGICAL HISTORY

No pertinent history

FAMILY HISTORY

No pertinent history

SOCIAL HISTORY

No pertinent history

MEDICATIONS

No pertinent history

ALLERGIES

No pertinent history

PHYSICAL EXAMINATION

Ulcerated 2.5x2.5cm plaque on the right temple with indurated borders and serosanguinous drainage.

LABORATORY RESULTS

Normal Results
CBC
CMP
QuantiFERON-Gold
HIV antigen & RNA
Urine Blastomyces and Histoplasma antigen
Superficial aerobic/anaerobic cultures

Abnormal Results
No pertinent results

IMAGING STUDIES
Normal chest X-ray

DERMATOPATHOLOGY
Histopathologic analysis of a punch biopsy of the lesion revealed a mildly acanthotic epidermis with some spongiosis. There were fragments of dermis that demonstrated dense plasmacytic infiltrate with intermixed histiocytes and scattered multinucleated giant cells. A giant cell reaction surrounding rare naked hair shafts and focal collections of neutrophils was also present. DPAS-F, Gram, Fite, and AFB stains were performed and negative. The stains were negative for infectious organisms. CD1a highlighted background Langerhans' cells but was negative for intracellular organisms. Antitreponemal antibody was negative.

MICROBIOLOGY
Fungal and AFB cultures identified the growth of gram positive aerobic actinomycetes, three weeks following initial culture. Next generation sequencing identified the organism as Nocardia nova.

DIAGNOSIS
Primary superficial cutaneous nocardiosis.

CLINICAL COURSE
Following consultation with infectious disease, treatment with oral TPM-SMX was begun with plans for a two-month course. At one-month follow up, the patient noted marked improvement in the wound and her clinical exam showed reepithelization of a well-healing plaque. She was instructed to continue TPM-SMX. Five weeks into therapy, the patient self-discontinued TPM-SMX due to continued noted improvement. One week following discontinuation, the patient experienced expansion of the wound with increased erythema, erosion, and drainage of the wound as well as a new similar lesion in the conchal bowl. The patient resumed TPM-SMX and is currently undergoing her second treatment course with plans for at least a 3-month course.

DISCUSSION
Nocardiae are gram-positive, branching, aerobic actinomyctes responsible for systemic illness in immunocompromised hosts and skin-limited infection in immunocompetent hosts.[1,2] Three clinical subtypes of primary cutaneous nocardiosis are described: lymphocutaneous infection, mycetoma, and superficial cutaneous infection; the latter representing our patient's form.[2]

Due to its rarity and diverse cutaneous features, nocardiosis is a challenging diagnosis to make. Superficial infection may take the form of ulcers, granulomas, abscesses, cellulitis, bullous lesions, linear/keloid-like lesions, and nodular-pustular lesions.[2,3] The clinical course is also variable - Lesions may occur suddenly and rapidly progress or remain dormant and slowly expand over years.[3] Cutaneous nocardiosis has been mistaken for lesions of sporotrichosis, atypical mycobacterial infections, leishmaniasis, and systemic lupus erythematosus, all of which were considered in our patient.[3]

Risk factors can be helpful when present and include soil or sand exposure, farming, superficial injuries from domestic shrubbery or motor vehicle accidents.[3] In most reported cases, patients are male and have a history of local trauma.[2] In rare cases involving children, the face is commonly affected, and a history of trauma may not be elicited.[3,4]

Isolating the organism in the laboratory is challenging and may lead to further diagnostic delays. In our patient's case, a prior superficial swab for gram stain and culture resulted negative and subsequent culture from biopsy required a three-week incubation period to identify colonies. In contrast to specimens obtained by biopsy, peripheral swab sent for smear and cultures of nocardiosis are positive in only one-third of cases, so specimens should be obtained by biopsy.[5] Clinicians should alert their laboratory when nocardial infection is suspected, and when possible, multiple clinical specimens should be submitted for culture, and plates should remain incubated for at least three weeks.[5,6]

Treatment is indicated for all patients with nocardiosis, and the treatment of choice remains TMP-SMX.[7] Our immunocompetent patient with superficial skin infection was treated for five weeks prior to self-discontinuation, and her infection quickly relapsed and subsequently spread. Relapses have been previously described in immunocompromised hosts.[8,9] Optimal duration of therapy is undetermined and largely guided by empirical studies. Treatment courses of 2-4 months is recommended for most cases of primary cutaneous nocardiosis in immunocompetent patients.[5, 8, 9]

KEY POINTS

- Primary cutaneous nocardiosis has a variety of clinical manifestations and should be considered for the atypical wound resistant to treatment
- Isolating *Nocardiae* can be challenging and time consuming; cultures should be obtained by biopsy, incubated for adequate durations, and repeated if suspicion remains
- Relapses of nocardiosis may occur with short treatment durations thus treatment courses of 2-4 months for immunocompetent patients are standard

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CHICAGO DERMATOLOGICAL SOCIETY

CASE #6

Presented by Emily Medhus, DO, Mariam Mafee, MD
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HISTORY OF PRESENT ILLNESS

A 15-year-old male presented to the dermatology clinic accompanied by his mother for evaluation of a "mole" on his penis. Although the patient referred to the lesion as a birthmark, his mother reported that the lesion was not present at birth. She believed that the lesion was new within the past year, but the patient was unsure when it first appeared. The lesion was asymptomatic, and the patient had not noticed any recent changes or growth.

PAST MEDICAL & SURGICAL HISTORY

Arachnoid cyst of the posterior fossa
Asymmetrical sensorineural hearing loss

FAMILY HISTORY

No family history of cutaneous malignancies or dysplastic nevi. No family history of Carney Complex.

SOCIAL HISTORY

High school student, lives at home with mother and maternal grandmother.
Denies tobacco use, drug use, and is not sexually active.

MEDICATIONS

Cyproheptadine 4 mg nightly
Ketoconazole shampoo twice weekly
Melatonin 3 mg nightly
Multivitamin daily

ALLERGIES

None

PHYSICAL EXAMINATION

Involving the right aspect of the glans penis was an asymmetric, black, amorphous macule with homogenous network on dermoscopy. There was a discontiguous satellite lesion along the inner prepuce.

LABORATORY RESULTS

None

DERMATOPATHOLOGY

A shave biopsy showed a dermal proliferation of heavily pigmented melanocytes that were epithelioid in morphology. Mitotic figures were not readily identified. Background melanophages were also noted. The melanocytes were highlighted by SOX10 stain and showed rare nuclear positivity with Ki-67 stain, imparting a proliferation index of less than 1%.

DIAGNOSIS
Pigmented epithelioid melanocytoma

CLINICAL COURSE
Given the location and size of the lesion, the patient was referred to pediatric urology for excisional biopsy under general anesthesia. The biopsy revealed a pigmented epithelioid melanocytoma, prompting interdisciplinary discussion at melanoma tumor board among the dermatology, surgical oncology, urology, and pathology teams. After discussion with the patient and his family, the decision was made to pursue wide local excision and sentinel lymph node biopsy.

Prior to surgical intervention, an ultrasound of the bilateral inguinal regions was done and revealed sonographically normal-appearing lymph nodes. Lymphangiogram showed no definite foci of uptake in the inguinal or pelvic region to suggest sentinel nodes.

Wide local excision was performed under general anesthesia by surgical oncology and pediatric urology. In addition to excision, circumcision was also performed given the satellite lesion on the prepuce. The margins for the wide local excision were 1 cm and the depth was down to the corpus cavernosum. Before closure, intraoperative frozen sections of the deep layer were obtained and were negative. The deep tissue and epithelium of the glans were then reapproximated with absorbable sutures. The sentinel lymph node biopsy from the right inguinal region was negative for malignancy.

The patient followed up with urology 1 month post-operatively and had well-healing surgical incisions. At that time, urology recommended routine surveillance with dermatology.

DISCUSSION
Pigmented epithelioid melanocytoma (PEM) is a rare and distinct entity within the spectrum of borderline/intermediate melanocytic tumors. It was previously referred to as animal-type melanoma prior to being reclassified under the name PEM. The term “pigmented epithelioid melanocytoma” was first suggested in 2004 to describe a histologic entity which encompassed both animal-type melanoma and epithelioid blue nevus.[1] Acceptance of the new terminology didn’t occur until 2018 when the World Health Organization strongly advised against using the term animal-type melanoma due to a potential source of confusion. Unlike traditional melanoma, PEM classically has an indolent course.[1] While lymph node metastasis and recurrence are common, visceral metastasis and death are exceptionally rare.[1] Currently, there is discrepancy in the literature regarding the clinical behavior and overall prognosis of PEM, and there are no universally agreed-upon guidelines for management.

PEM typically presents as a solitary pigmented lesion in the skin. The lesions are blue-black, deeply pigmented, papules or nodules and may have an asymmetric shape or pigment distribution.[1,2] Due to their clinical appearance, these lesions are often biopsied to rule out melanoma. PEM’s may arise anywhere on the body but commonly occur on the extremities.[2,3] Rarely, PEM may involve the oral or genital mucosa. Interestingly, of the reports describing PEM in male genitalia, many involve the glans penis specifically, as seen in our patient.[4]

Histologically, PEM is characterized by large, heavily pigmented, epithelioid and/or spindled melanocytes forming nests and sheets within the dermis.[5] The lesions overall architecture is wedge-shaped and symmetric. Melanophages are often present. There may be signs of cellular atypia, including nuclear pleomorphism and mitotic activity, which raises concerns about malignant potential, yet the overall behavior tends to be more indolent than malignant melanoma.

PEM exhibits various genomic subtypes that offer insights into its pathogenesis and clinical behavior. One notable subtype involves PRKAR1A inactivating mutations, often in conjunction with BRAF mutations. This subtype is seen in the combined type of PEM, in which there is an associated nevus on histology.[2] Lesions with this mutation also occur in the context of Carney Complex. Conversely, PEMs characterized by PRKCA fusion tend to manifest as pure lesions, i.e., without an associated nevus.[2] This mutation implies a stable lesion with low risk of malignant transformation, as PRKCA fusions are exceptionally rare in melanoma.[2] A PEM with this mutation predicts favorable prognosis with minimal risk of metastasis.[2] GNAQ mutations in PEM confer similarities with blue nevi, but with a more pronounced epithelioid morphology.[2] Additionally, a subset of PEMs harboring NTRK3 fusions alongside PRKAR1A mutations typically exhibit a predominant spindle cell morphology, further highlighting the genetic heterogeneity within this entity.[2]

Given its rarity and potential for diagnostic confusion with other melanocytic lesions, accurate diagnosis is crucial for appropriate management. Surgical excision remains the treatment of choice, but guidelines regarding margin size are lacking. Some clinicians approach it similarly to melanoma, with margins based on Breslow depth. Others argue that wide margins are unnecessary given the low-grade nature of PEM.[6] In most cases, surgical excision is curative.

There is also a lack of consensus regarding the role of sentinel lymph node biopsy (SLNB). PEM is known to have a high rate of regional lymph node metastasis (40-50%); however, the presence of nodal metastasis has not been shown to impact prognosis, nor does it predict distant metastatic disease.[3,7,8] There are rare reports of visceral metastasis, most of which involve the liver.[1,9] This information could help guide screening tests and monitoring for metastasis. While most PEMs follow a relatively benign course, close clinical follow-up is recommended due to the limited understanding of its natural history and potential for metastasis and recurrence.

In summary, pigmented epithelioid melanocytoma represents a distinct subtype of melanocytic tumors characterized by its unique histopathological features and relatively indolent behavior. Continued research efforts are needed to better understand the underlying biology of PEM and to optimize diagnostic and therapeutic strategies for affected patients.

KEY POINTS

- Pigmented epithelioid melanocytoma is a unique melanocytic neoplasm due to its indolent clinical course but reportedly can have high rate of nodal metastasis and recurrence.
- Histologic findings include heavily pigmented epithelioid, dendritic, and/or spindled melanocytes forming nests and sheets within the dermis.

- Surgical excision is the treatment of choice but there is no consensus regarding margin size and if/when to perform sentinel lymph node biopsy.
- Potential for aggressive behavior should not be overlooked.

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CHICAGO DERMATOLOGICAL SOCIETY

CASE #7

Presented by Alexandra Eckburg, MD; Claudia Hernandez, MD, MEHP
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HISTORY OF PRESENT ILLNESS

A 65-year-old male presented to dermatology clinic for evaluation of a new rash. Fourteen months prior to presentation, patient had wrist surgery with orthopedics. No hardware was placed, and the patient had been wearing a wrist split daily since then. Fourteen months later, patient presented to his PCP with new sores, drainage, and erythema of 3 weeks duration. These findings were localized to the area underneath the wrist brace. He had been applying hydrogen peroxide and an over the counter antibiotic ointment without improvement. His primary care physician ordered a wrist X-Ray, ESR, CRP, and CBC to rule out of osteomyelitis. His workup was negative and he was referred to dermatology.

During our encounter, patient reported that the rash was primarily localized to the area underneath his brace, but he also had red bumps extending to his forearm. He endorsed significant pain. He denied the following: pruritus; owning pets including fish; chemical or construction exposure; and gardening.

PAST MEDICAL & SURGICAL HISTORY

Asthma, Non-Hodgkin Lymphoma treated through Port Rituximab, Cyclosporine, Hydroxydaunorubicin hydrochloride , Vincristine, Prednisone and RT in remission since 2007

FAMILY HISTORY

No known family history.

SOCIAL HISTORY

Smokes one pack of cigarettes daily.

MEDICATIONS

Multivitamin, Cyanocobalamin 1,000 mcg, Ascorbic Acid 1,000 mg, Calcium Carbonate/Vitamin D3

ALLERGIES

None

PHYSICAL EXAMINATION

Right dorsal wrist - An erythematous plaque with fissuring, fine scale, and ulceration; erythematous, tender nodules were present on the mid forearm in a sporotrichoid pattern. No palpable lymphadenopathy.

LABORATORY RESULTS

CBC with differential- normal
CMP- normal
HIV- negative
AFB Culture- negative
Fungal Culture- negative

IMAGING STUDIES
None

PATHOLOGY
Histopathologic analysis of a punch biopsy specimen taken from a nodule on the mid- forearm demonstrated the following.

The epidermis was not involved. The tumor was composed of large cells perivascular zonation, and the deeper areas in the subcutis showed extensive necrosis. The tumor cells were strongly positive for CD30, showed moderate CD2 expression, moderate aberrant CD15 expression, and occasional CD8 expression. They were negative for P63, ALK1, CD3, CD7, EBER, CD4, CD20, PAX5, CD68 (KP-1, which highlights admixed histiocytes). CD5 stained rare large cells. PAS, GMS, Gram, and AFB stains were noncontributory.

Additional stains performed at NeoGenomics lab showed that the tumor cells are weakly to moderately positive for Bob1 and negative for Oct2 and TCRBf1. Despite the unusual location and expression of T cell markers, expression of Bob1 is considered strong indication of B lymphocyte lineage identity and a diagnosis of classic Hodgkin lymphoma rather than anaplastic large T cell lymphoma.

DIAGNOSIS
Cutaneous Presentation of Systemic Hodgkin Lymphoma

CLINICAL COURSE
The patient was referred to hematology-oncology who completed the malignancy workup. His CBC was WNL except for lymphocytes of 11.8%; CMP notable CO2 21, Cr 1.28, albumin of 3.3; LDH normal at 233. PET CT Scan was notable for abnormally enlarged and hypermetabolic right axillary lymph node concerning for nodal metastatic disease. It was recommended that the patient undergo an ultrasound-guided percutaneous biopsy.

Imaging was also notable for abnormal mildly hypermetabolic activity seen in the right lower lobe corresponding to an area of minimal ground glass attenuation and minimal nodularity. This lesion is likely related to inflammation or infection, however, developing metastatic lesion could not be excluded. In addition, there was a 5mm left upper lobe nodule without significant hypermetabolic activity. This lesion was indeterminate for both metastatic disease versus primary lung cancer given background centrilobular emphysema. Follow-up of both lesions was recommended.

Oncology determined the patient had advanced stage Classic Hodgkin Lymphoma, Stage IV, Hassenclever IPS score 4. It was recommended that the patient begin treatment with BV (brentuximab-vedotin) and AVD (adriamycin, vinblastine, decarbazine). He received his first dose of brentuximab on 10/20/23. After which, he transferred care to an oncologist at an outside hospital and is no longer being seen by Rush.

DISCUSSION
Hodgkin lymphoma is a malignancy of the lymphatic system and is subdivided into classical Hodgkin lymphoma and nodular lymphocytic predominant Hodgkin lymphoma. Together, they account for 10% of cases of newly diagnosed lymphoma in the US. [1] There is a slight predilection for male gender (56%), and the median age of diagnosis is 39 years old with a

bimodal peak. [1] The first incidence peak is between the ages of 20 and 30 years old, with a second peak between 50 and 70 years old.[2] Early stage prognosis is quite good and >90% of patients with early-stage classical Hodgkin lymphoma achieve cure. Patients are more likely to die from long-term treatment complications than from the disease itself. [1]

Classical Hodgkin lymphoma is composed of malignant Reed-Sternberg cells along with a surrounding reactive inflammatory and immune cell infiltrate. [2] Reed-Sternberg cells, which derive from germinal center B-cells, create a unique network of cellular proliferation, inhibition of apoptosis, and suppression of cytotoxic killer cells. These changes are potentially due to constitutively expressed JAK/STAT signaling and possibly clonal presence of Epstein-Barr Virus. They evade antitumor immune responses via alterations in the genes encoding PD-1 receptor ligands PD-L1 and PD-L2. These cells are characterized by abundant basophilic or amphophilic cytoplasm and a binucleated or bilobed nucleus, which expresses CD30, CD15, CD20, and, PAX5. [2]

A common presentation of HL is unremitting pruritis and/or painless lymphadenopathy. B symptoms are frequent in patients with advanced-stage or bulky disease and are considered prognostic. [2]

Previously, there had been thought that primary cutaneous HL was a distinct, albeit rare, entity. However, this idea is no longer accepted, and these cases are now understood to be a part of anaplastic large cell lymphoma. When cutaneous involvement of HL is present, it always represents skin dissemination of systemic disease. [3] Typically, cutaneous involvement is a result of severe, advanced systemic disease, usually by direct extension to skin from affected lymph nodes. Advances in treatment with chemotherapy, radiation, targeted agents, immunotherapies, and hematopoietic stem cell transplants have led to an overall reduction in cutaneous disease. It is estimated that cutaneous involvement occurs in only 0.5-3.4% of Hodgkin lymphoma cases. [4]

Currently, there are scattered reports of cutaneous involvement being a primary presentation of HL.[4, 5, 6, 7] In these case reports, patients first presented with concerning skin lesions and were diagnosed with HL upon skin biopsy, similar to our patient. More typically, patients present with systemic symptoms and only upon further evaluation are they found to have cutaneous involvement. These patients tend to have more advanced disease at first diagnosis.[3] Of those patients with an initial presentation of cutaneous disease, all were responsive to standard chemotherapy and achieved remission with treatment.

As discussed above, the previous cases of primary cutaneous Hodgkin lymphoma are now better understood as ALCL. If a patient presents with Hodgkin lymphoma in the skin, it is always indicative of underlying systemic disease. The prognosis of Hodgkin lymphoma, however, is good, and many patients achieve cure with chemotherapy, but early initiation of treatment is critical to achieve these positive outcomes.

KEY POINTS

- Primary cutaneous Hodgkin Lymphoma is no longer a recognized entity
- Cutaneous involvement of Hodgkin lymphoma is always a sign of systemic disease
- Overall prognosis of Hodgkin lymphoma is good and it is the only malignancy that is considered cured with chemotherapy.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE #8**

Presented by Rachel Lefferdink, MD and Marie D. Lafeir, MD
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HISTORY OF PRESENT ILLNESS

A 55-year-old woman with recent diagnosis of hyperthyroidism presented to the emergency department with worsening bilateral lower extremity ankle and foot pain, erythema and swelling. Her symptoms started approximately 10 days prior to presentation and her pain continued to worsen to the point she was unable to stand or ambulate.

The patient noted she first experienced swelling of her bilateral feet (not painful at that time), weight loss (patient estimated 50 lbs), fatigue, anorexia, malaise and hair loss in late July 2023. In August 2023, her PCP diagnosed her with hyperthyroidism and started her on methimazole after finding undetectable TSH levels, elevated free thyroxine and positive TSH receptor antibodies. Approximately one month later she started to experience erythema, edema, and pain in her ankles and feet. She subsequently developed bilateral wrist and hand stiffness, as well as erythema and tenderness of the left wrist. She also endorsed subjective fevers, chills, and night sweats. She presented to her PCP and was started on a course of cephalexin. When her symptoms continued to worsen despite antibiotics, she presented to the Rush emergency department for further evaluation.

She had no recent travel history but previously spent a lot of time at her family's cabin in southern Illinois, although she had not been there in the past 1.5 years.

PAST MEDICAL & SURGICAL HISTORY

The patient denied other personal history of autoimmune disease and never had similar symptoms previously.

The patient reported she was always healthy prior to her current presentation. She had not had a mammogram or other cancer screenings in many years because she had always been feeling well.

FAMILY HISTORY

Sister with history of rheumatoid arthritis.

SOCIAL HISTORY

No pertinent history

MEDICATIONS

Methimazole 5 mg daily
Multivitamin

ALLERGIES

No known allergies

PHYSICAL EXAMINATION

Significant pitting edema, deep erythema and exquisite tenderness to palpation of the bilateral ankles and dorsal feet.

Mildly erythematous, tender nodules involving the left dorsal wrist.

Firm, mildly tender subcutaneous mass with minimal overlying erythema on the right lateral thigh.

Alopecic patches involving the vertex scalp without erythema, scale, or scarring.

No lymphadenopathy on exam.

LABORATORY RESULTS

Basic

CBC: normocytic anemia (Hb 9.2 g/dL, MCV 81.8 fL), thrombocytopenia (platelets 479 K/uL)
Ferritin: elevated (545 ng/mL)
Haptoglobin: elevated (359 mg/dL)
CMP: normal
LDH: normal
ACE: normal
Folic acid: normal
Vitamin B12: normal

Inflammatory

CRP: elevated (187.4 mg/dL)
ESR: elevated (126 mm/hr)

Endocrine

TSH: suppressed (<0.008 iIU/mL)

Autoimmune

ANA screen: negative
Rheumatoid factor: normal
C3/C4: normal
Anti-histone antibody: normal
ANCAs: (C-ANCA 1:20, others normal)

Infectious

Quantiferon TB Gold Plus: negative
HIV antigen/antibody: negative
HCV antibody: negative
Syphilis total treponemal antibody screen: non-reactive
Urine Chlamydia Trachomatis/Neisseria Gonorrhea RNA probe: negative
Parvovirus B19 antibody: negative
Q fever (Coxiella burnetti) antibody screen: negative
Spotted Fever Group antibody panel: negative

Enterovirus RNA PCR: not detected
Cryptococcal antigen: not detected
Histoplasma antigen: not detected
Coccicioides antigen: not detected
Bartonella antibody panel: negative
Brucella antibody panel: negative
Blastomyces antibody: negative
Galactomannan antigen (Aspergillus): negative
Beta-d-glucan assay: negative
ASO titer: elevated → GAS throat culture: negative

Neoplastic
SPEP: ambiguous results → immunofixation electrophoresis: possible monoclonal IgG Kappa

IMAGING STUDIES
X-rays of bilateral feet and ankles (3 or more views):
No acute displaced fracture. Alignment appears satisfactory. Diffuse soft tissue swelling most marked over the dorsum of the foot. No radiographic evidence of significant ankle joint effusion. No unexpected radiopaque foreign body. No acute osseous abnormalities.

CT Chest w/ Contrast:
Multiple enlarged mediastinal and bilateral hilar lymph nodes.
Few scattered ground-glass opacities in the left lower lobe concerning for evolving versus resolving multifocal infection.
Edematous gallbladder wall. Focal fatty infiltration of the left hepatic lobe.

PATHOLOGY
Punch biopsy of right ankle:
H&E showed granulomatous septal panniculitis suggestive of erythema nodosum.
PAS, GMS and Fite stains negative for microorganisms.

Lymph node biopsy:
Heterogeneous population of lymphoid cells and rare granulomas, consistent with a reactive lymph node. The specimen was negative for malignant cells.
GMS, PAS, and Fite stains were negative for fungal forms and acid-fast bacilli.

MICROBIOLOGY
Peripheral blood cultures x 4: No growth

Tissue culture (punch biopsy of right ankle): No growth of aerobic, anaerobic, fungal or acid-fast bacilli cultures

Tissue culture (hilar lymph node biopsy): No growth of aerobic, anaerobic, fungal or acid-fast bacilli cultures

Bronchial washings: No growth of AFB and fungal cultures; mycobacterium tuberculosis PCR negative

DIAGNOSIS
Lofgren Syndrome

CLINICAL COURSE
In consultation with infectious disease and rheumatology, systemic steroids were initially held due to concern for infectious etiology of the patient's symptoms. By the time the patient underwent bronchoscopy with bronchoalveolar lavage and lymph node biopsy, and those results and other laboratory evaluations had finalized, the patient had rapidly improved. Throughout her hospitalization, her pain was controlled with ibuprofen, gabapentin and hydrocodone with acetaminophen. By discharge, her ankle swelling lessened, she was able to ambulate without significant pain, and her subcutaneous nodules had either decreased in size or resolved. At 6-month follow up she no longer had any cutaneous or articular symptoms with only some post-inflammatory hyperpigmentation of the feet and ankles.

DISCUSSION
Lofgren Syndrome is a subtype of sarcoidosis first described by Swedish pulmonologist Sven Lofgren during the mid-20th century.[1] It is a self-limited type of sarcoidosis that presents with the specific triad of hilar lymphadenopathy, acute arthritis and erythema nodosum (95% specific).[2] Fever is also common. The acute onset of symptoms distinguishes Lofgren syndrome from typical sarcoidosis, which usually has an insidious onset. In addition, the most common cutaneous finding in Lofgren Syndrome is erythema nodosum (seen in anywhere from 57% to 100% of cases)[3] and granulomatous skin involvement is usually absent. This is contrast to typical sarcoidosis, in which the skin is the second most common organ after the lungs to be affected by granulomatous lesions (found in approximately one third of cases).[4] In Scandinavian countries, Lofgren Syndrome makes up approximately one third of all sarcoidosis cases, while it represents less than one percent of sarcoidosis cases in the United States.[1]

The triad of symmetrical ankle arthritis, erythema nodosum and an acute onset of less than two months is 99% specific for a diagnosis of Lofgren syndrome.[5] Symmetric ankle involvement alone is 95% specific and seen in 75-100% of patients.[5] Given the high specificity of the clinical findings, most experts agree that histologic confirmation is not required to make the diagnosis.[1] However, should the patient's presentation deviate from the classic findings, further workup and histopathologic correlation is required.[6] In terms of additional testing, a chest x-ray demonstrating hilar lymphadenopathy helps confirm the diagnosis, otherwise no specific tests are required. Laboratory evaluations demonstrating elevations in C-reactive protein (CRP), calcium, acetyl cholinesterase (ACE), alkaline phosphatase, and polyclonal gamma globulins also support the diagnosis.[6]

Lofgren syndrome patients are well-documented to have a good prognosis. Most cases are self-limited with > 90% showing full resolution within 2 years.[6] This is especially true for HLA-DRB1*03+ individuals,[1] which is a major genetic risk factor for systemic lupus erythematosus, as well as predisposing for Lofgren Syndrome. The disease course may be more prolonged in individuals without this predisposition.[7] While no treatment is required for Lofgren Syndrome, NSAIDs can be helpful to control symptoms. Colchicine or systemic steroids can be used in severe cases.[2] Periodic repeat chest x-rays can be used to assess for complete resolution if clinically necessary.

Sarcoidosis is not uncommonly associated with autoimmune diseases, especially with autoimmune thyroid disease.[8] A common immunopathogenesis has been proposed to explain this association.[9] Prior matched case-control studies have reported a range of 12% to 50% of sarcoidosis patients with autoimmune thyroid disease.[9] Hypothyroidism is more commonly associated than hyperthyroidism.[10] The association may be more common in patients with Lofgren Syndrome versus typical sarcoidosis. In a small study of patients with sarcoidosis (n = 10) and autoimmune thyroid disease, 80% of these patients presented with Lofgren syndrome.[11] This has led some experts to encourage the use of thyroid function testing in sarcoidosis patients,[10] especially those presenting with acute arthritis.[12]

KEY POINTS

- Consider Lofgren Syndrome as a diagnosis in patients with bilateral ankle swelling and arthritis.
- Clinical features of Lofgren Syndrome are highly specific and do not require histologic confirmation to make the diagnosis.
- There may be a role for thyroid function testing in patients with clinical features consistent with Lofgren Syndrome.

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