PROTOCOL BOOK • OCTOBER 11, 2023

CHICAGO DERMATOLOGICAL SOCIETY 2023

Monthly Meeting

Co-hosted by University of Illinois at Chicago Department of Dermatology

Chicago Dermatological Society

PROTOCOL BOOK
October 11, 2023

Co-hosted by
University of Illinois at Chicago Department of Dermatology

Guest Speaker: **Jacqueline Watchmaker, MD**
Board-Certified Dermatologist
Center for Aesthetic and Laser Medicine, Scottsdale, AZ

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INVITED GUEST LECTURER

Jacqueline Watchmaker, MD

Dr. Jacqueline Watchmaker is a Board-Certified Dermatologist who practices medical, procedural and cosmetic dermatology. She currently practices at the Center for Aesthetic and Laser Medicine, Scottsdale. Dr. Watchmaker is originally from Wisconsin and earned her medication degree from Medical College of Wisconsin. In medical school she was elected to the prestigious Alpha Omega Alpha Honor Society. Following medical school, she completed a one-year internal medicine internship where she was selected as the “Best Intern” for her year. She then completed dermatology residency at Boston University in Massachusetts where she served as chief resident during her final year.

Following residency Dr. Watchmaker was accepted to a Laser and Cosmetic Dermatology fellowship the at Skincare Physicians in Chestnut Hill, Massachusetts. In fellowship she developed expertise in the use of injectable fillers, neuromodulators, lasers and other energy-based devices for the treatment of many conditions including rosacea, acne, birthmarks, scarring, ageing skin, cellulite, hair loss and melasma.

Dr. Watchmaker has written multiple book chapters and published many research papers in peer-reviewed medical journals. The majority of her research focuses on the use of lasers in dermatology. Dr. Watchmaker has presented at many national and international meetings including the American Academy of Dermatology, the American Society for Dermatologic Surgery, International Society of Dermatology, World Congress of Dermatology and the American Society for Laser Medicine and Surgery.

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PROGRAM

Co-hosted by
University of Illinois at ChicagoDepartment of Dermatology

October 11, 2023
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** 1.Approaching the Aging Face 2.Optimizing Melasma Treatment in 2023: Drugs, Lasers and Cosmeceuticals *Jacqueline Watchmaker, 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** 3. How to Treat Scars: A Case Based Discussion 4. Interesting Aesthetic Cases *Jacqueline Watchmaker, MD*
2:00 p.m.	*Program adjourns*

University of Illinois at Chicago
Department of Dermatology

Chicago Dermatological Society Meeting
October 11, 2023

Dermatology Residents

Fourth Year
Brian Cahn, MD
Neha Chandan, MD
Victoria Kuritza, MD
Carolina Puyana, MD

Third Year
Ryan Bunney, MD
Samantha Hunt, MD
Christine Pak, MD
Jane Zhang, MD

Second Year
Allison Ellis, MD
Yoni Hirsch, MD
Alex Woods, MD
Lacey Zimmerman, MD

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8:00 a.m. - 2:00 p.m.
Resident Case Presentations & Discussion

Case Presented by Samantha Hunt, MD
Timothy Tan, DO, Kyle Amber, MD, and Sheryl Hoyer, MD

History of Present Illness:
A 39-year-old male who was previously lost to follow up with dermatology after undergoing workup for a generalized bullous disease presented to re-establish care for a separate concern. The patient reported a few months' history of erythematous, scaling plaques over his face, torso, upper and lower extremities, hands, and feet. He had been seen in the emergency room intermittently over the last few years for a similar rash, which was treated as psoriasis, but he had not previously followed with a dermatologist or primary care physician for this concern.

Further chart review did reveal he had previously seen a dermatologist for an acute onset, generalized bullous disease three years prior. The patient had presented with bullae over most of his torso and bilateral upper and lower extremities. Workup at that time with H&E, direct, and indirect immunofluorescence was consistent with a subepithelial immunobullous disease with dermal reactivity such as epidermolysis bullosa acquisita (EBA), anti-p200 pemphigoid, anti-laminin-332 pemphigoid, or bullous lupus erythematosus. Pemphigus panel, anti-type VII collagen antibody by ELISA, IgA pemphigus panel, and anti-nuclear antibody were all negative. Given the patient's noted extensive clinical presentation in the setting of negative serology for collagen VII antibodies, the clinical history favored a diagnosis of anti-p200 pemphigoid. He was treated with methylprednisolone, doxycycline, and dapsone, but was lost to follow-up.

Past Medical History:
None

Medications:
None

Allergies:
NKDA

Family History:
Non-contributory

Physical Examination:
Physical exam of the patient at presentation revealed only diffuse, erythematous plaques with fine scale over his face, chest, back, arms, legs, hands, and feet. There were no active vesicles or bullae on exam.

Histopathology:
1. Skin, left arm, perilesional, DIF: Homogenous, linear staining of IgG and C3 in the basement membrane zone. The staining is present in the floor side in blister areas.
2. Skin, left arm, H&E: Subepidermal neutrophil-rich blister.
3. Skin, back, H&E: Psoriasiform dermatitis.

Labs and Imaging:
Pemphigoid panel: Positive IgG and IgG4 reactivity in a dermal pattern on human split skin substrate.

Pemphigus panel, anti-collagen VII antibody by ELISA, IgA pemphigus panel, and anti-nuclear antibody were all negative.

Diagnosis:
Co-existing psoriasis and anti-P200 pemphigoid

Treatment and Course:
Our patient was initially treated with dapsone for his bullous disease, however the patient was lost to follow-up. When the patient presented again, a repeat biopsy was done and was consistent with psoriasiform dermatitis. He was treated with mycophenolate mofetil and methylprednisolone to prevent the recurrence of bullous outbreaks as well as topical steroids for his active psoriatic lesions. Dapsone was not resumed due to anemia noted on outside labs. At follow-up, he was significantly better and transitioned to methotrexate, a more typical treatment for psoriasis. He remains free of active bullous disease.

Discussion:
The coexistence of psoriasis and autoimmune bullous diseases (AIBDs) has been well-reported in the literature. The first documented case describing the coexistence of these two entities dates back to 1929. Since then, there have been multiple epidemiological studies performed that have shown an increase in the incidence of AIBDs in patients with psoriasis. The most commonly reported association is that of psoriasis and pemphigoid diseases. Of the pemphigoid group of AIBDs, bullous pemphigoid is most reported to occur in patients with psoriasis. A case series evaluating 145 cases of patients with coexisting psoriasis and AIBDs found the majority of cases were complicated by bullous pemphigoid (63%), anti-p200 pemphigoid (37%), or a combination (8%). Other AIBDs reported to have some association with psoriasis include pemphigus, most notably pemphigus foliaceus, linear IgA bullous dermatosis, and epidermolysis bullosa acquisita.

The first case of anti-p200 pemphigoid associated with psoriasis was reported by Chen et al. in 1996. At that time, a patient with a known history of psoriasis presented with bullae formation over their psoriatic lesions as well as on uninvolved skin. Further workup with both direct and indirect immunofluorescence was not consistent with bullous pemphigoid or any other autoimmune bullous disease previously identified. Through further analysis, Chen et al. were the first to detect a novel autoantibody against a 200-kDa dermal protein localized in the lower lamina lucida of the basement membrane zone (BMZ). They described this clinical entity, which later became known as anti-p200 pemphigoid, as distinct from other AIBDs and hypothesized an association with psoriasis.

The true prevalence of anti-p200 pemphigoid is unknown. This is due, in part, to the fact that tests to detect the anti-laminin λ-1 antibody are not commercially available in many countries. Therefore, it is hypothesized that many cases are undiagnosed. In fact, some researchers believe many cases of anti-p200 pemphigoid may have previously been

misdiagnosed as EBA. Although its prevalence may not be well understood, since its discovery, there has been much data to support anti-p200 pemphigoid's association with psoriasis. In fact, psoriasis has been noted in about 30% of published cases of anti-p200 pemphigoid.
The reasoning for an association between psoriasis and anti-p200 pemphigoid is not well understood. An underlying genetic contributor may play a role as certain human leukocyte antigen (HLA) alleles and susceptibility genes have been associated with psoriasis. However, none of these genetic markers associated with psoriasis have been found to also be associated with most AIBDs. It is hypothesized that the underlying inflammation within psoriatic lesions themselves may trigger antigen exposure and auto-antibody formation leading to bullae formation. For instance, the neutrophilic infiltrate in psoriatic lesions releases matrix metalloproteases that degrade multiple targets, including laminins. Degradation of laminin also occurs from an increased amount of $\alpha 5 \beta 1$ integrin, fibronectin, and plasminogen activators in psoriasis. This increased exposure of degraded laminin is hypothesized to trigger the production of autoantibodies to laminin λ-1 eventually leading to anti-p200 pemphigoid.

Patients with anti-p200 pemphigoid typically present with tense bullae and urticarial plaques, often associated with pruritus. Lesions are typically noted on acral sites; however, involvement of the trunk, extremities, and mucous membranes has been noted. Such lesions may occur over psoriatic plaques or over uninvolved skin. Psoriasis vulgaris is the most common type of psoriasis in such patients followed by pustular psoriasis and then erythrodermic psoriasis. Psoriasis has been noted to typically precede the diagnosis of anti-p200 pemphigoid in these patients, with a mean time of 15.1 years elapsing before patients are diagnosed with the AIBD. The mean age of onset in anti-p200 pemphigoid patients is younger (65.5 years) as compared to patients with bullous pemphigoid. Additionally, men are more likely to be affected by anti-p200 pemphigoid with coexisting psoriasis than females at a ratio of 7.7:1.

A standard treatment regimen for psoriasis and anti-p200 pemphigoid has not been identified. Effective monotherapies that have been reported in the literature include topical corticosteroids, systemic corticosteroids, minocycline, and dapsone. Of these, the most utilized treatment has been systemic corticosteroids at a dose of about 40-60mg of prednisolone daily However, recurrence of disease has been noted to occur during tapering of systemic steroids. In fact, a systematic review of patients with anti-p200 pemphigoid found that 39.6% of patients have at least one flare over the course of their disease and recommends systemic corticosteroids in conjugation with an adjuvant agent for long-term disease control. Adjuvant therapies noted to be effective include dapsone, long-acting tetracyclines, cyclosporine, azathioprine, mycophenolate mofetil, intravenous immunoglobulins, methotrexate, colchicine, plasmapheresis, and rituximab. Dapsone has been noted to be the most commonly used and effective treatment in anti-p200 pemphigoid patients, possibly due to its known efficacy among neutrophil-mediated conditions. Some patients may have flares of psoriasis after control of their bullous disease, which may be treated with topical steroids.

We describe this case of psoriasis occurring with anti-p200 pemphigoid to highlight the presentation of a rare, possibly underdiagnosed, autoimmune bullous disease and to bring attention to its association with psoriasis, which may help aid clinicians in diagnosing this condition but also presents an interesting challenge in management.

Essential Lessons:

- Consider anti-p200 pemphigoid as a differential diagnosis in patients presenting with a new onset autoimmune bullous disease who also have a history of psoriasis.
- Effective long-term management of patients with anti-p200 pemphigoid and psoriasis includes a regimen of systemic corticosteroids plus an adjuvant therapy to prevent relapse, most notably Dapsone.
- Considerations for workup and differential diagnoses:
    - Cutaneous inflammatory bullous dermatosis +/- minor mucosal involvement, DIF +, IIF + on dermal side (with high titer), COL7 ELISA -: favors anti-p200 pemphigoid
    - Cutaneous inflammatory bullous dermatosis +/- minor mucosal involvement, DIF +, IIF + on dermal side (with high titer), COL7 ELISA +: favors EBA
    - Seronegative EBA is generally pauci-inflammatory clinically
    - Laminin-332 pemphigoid is generally mucosal predominant with a prominent laryngopharyngeal component

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Case Presented by Alexander Woods MD
Wenhua Liu MD, Roger Haber MD

History of Present Illness:
In November of 2022, a 73-year-old male presented to the UIC dermatology clinic for an asymptomatic persistent rash on his right flank that started in 2009. Skin biopsy at that time was consistent with erythema annulare centrifugum. He then presented to UIC in September of 2018 due to worsening of the same rash. A skin biopsy was again performed and was consistent with a diagnosis of Majocchi granuloma. The patient was treated with terbinafine 250 mg daily for 3 months without significant improvement, followed by fluconazole 200 mg daily for two months with minimal improvement. Re-biopsy was planned, but the patient was subsequently lost to follow up until he represented in 2022. At this time, the patient states he was unable to identify any triggers or aggravating and alleviating factors. He had been applying clobetasol ointment on and off to the rash without significant improvement. He denied any fatigue, fevers, night sweats, or weight loss.

Past Medical History:
Ocular rosacea, hypertension, GERD, hyperlipidemia, kidney stones, and BPH. No personal or family history of skin cancer.

Medications:
Benazepril, dutasteride, hydrochlorothiazide, omeprazole, pravastatin, ezetimibe, tamsulosin.

Allergies:
No known drug allergies.

Social History:
Cigar smoker, occasional alcohol use.

Review of Systems:
The patient denied any fevers, chills, night sweats, weight loss, dyspnea.

Physical Examination:
11/2022: Right lateral chest/flank/back with indurated erythematous polycyclic, annular, serpiginous plaques, some with central clearing. No cervical, supraclavicular, or axillary lymphadenopathy present.

2/2023: Right lateral chest/flank/back same as above, now with 2 pink firm indurated nodules not evident at last visit. Left flank with similar pink to erythematous annular plaques, less well-demarcated.

Histopathology:
11/2022: Right flank, punch biopsy: atypical lymphocytic infiltrate suspicious for cutaneous B-cell lymphoma, with clonal population of B-cells. External dermatopathological review was concerning for cutaneous DLBCL (report describes

large cells), although definitive diagnosis was limited by sample; immunophenotype, B-cell origin, and Ki-67 > 90% were also consistent with the diagnosis of DLBCL.

2/2023: Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) of non-germinal center B-cell (non-GCB) type, negative for MYC rearrangement.
Superficial and deep lymphoid infiltrate. The cells show nuclear enlargement with small nucleoli and scant amounts of cytoplasm. There are admixed smaller lymphocytes. The overlying epidermis appears to be spared. The lesional cells are positive for CD20, BCL6, and MUM-1. C-Myc immunostaining is positive in approximately 25% of the cells. Ki-67 immunostaining shows an elevated proliferative index. The lesional cells are negative for Cyclin D1, CD30, CD10, BCL2, CD3 and CD5. A patchy peri-vascular lymphoid infiltrate composed predominantly of small lymphocytes with some admixed larger cells. These large cells are positive for CD20, while CD3 immunostaining highlights background small T cells.

In addition, FISH testing for MYC rearrangements and/or amplification, BCL6 and BCL2 rearrangements, and chromosome 8,14 translocation were all negative. The tumor was negative for Epstein-Barr virus DNA.

Diagnosis:
Primary cutaneous diffuse large B-cell lymphoma (DLCBCL), non-germinal center B-cell (non-GCB) type, not otherwise specified.

Treatment and Course:
Bloodwork including CBC, CMP, LDH were within normal limits. Staging PET scan with focal nodular attenuation in subcutaneous soft tissues in the right upper back at level of right scapula; also, with 2 foci of mildly increased FDG uptake in the posterior lateral right flank; no FDG avid lymph nodes above or below the diaphragm; no evidence of systemic disease. Patient was referred to hematology/oncology, who recommended R-CHOP x6 cycles with growth factor support. Patient deferred systemic therapy, electing for radiation therapy instead. To date, he has undergone one fraction of radiation therapy to the right flank and lateral chest lesions with significant improvement.

Discussion:
Diffuse large B-cell lymphomas (DLBCL) are aggressive malignant neoplasms that most commonly present in lymph nodes, but can present primarily (pcDLBCL) or secondarily on the skin.[1] When presenting primarily on the skin, they must be distinguished from other primary cutaneous B-cell lymphomas (pcBCLs), namely primary cutaneous follicle center lymphoma (pcFCL) with a diffuse growth pattern and primary cutaneous diffuse large B-cell lymphoma, leg type (pcDLBCL-LT). In the rare circumstance when an entity cannot be characterized as either of these according to the 2018 WHO-EORTC classification, a diagnosis of primary cutaneous diffuse large B-cell lymphoma – not otherwise specified (pcDLBCL-NOS) is made.[2,3]

pDLBCL-NOS is an exceedingly rare cutaneous lymphoma that is the subject of controversy and lacks consistent characterization in the literature to date. While not a formal entity in the 2018 WHO-EOTC classification, it's differentiation from pcDLBCL-LT and PCFCL diffuse growth may be of prognostic value with treatment implications.[4–6] pcFCL is characterized by indolent growth and an excellent prognosis with 5-year-

survival rate of more than 95%, while pcDLBCL-LT is characterized by aggressive growth with a poor prognosis of 5-year-survival rate of ~50%.[2] pcDLBCL-NOS appears to have a more moderate clinical course than pcDLBCL-LT.[6] Stratification using Hans's algorithm further classifies these tumors into postulated cell of origin germinal center B-cell (GCB) type and non-GCB type, based on CD10, BCL6, and MUM1 expression; with pcDLBCL-NOS, non-GCB being associated with more aggressive behavior and worse outcomes than GCB type, and similar although less aggressive than pcDLBCL-LT.[5]

pcBCLs overall comprise 20-30% of primary cutaneous lymphomas. The vast majority of pcBCL cases fall within the diagnostic categories of primary cutaneous marginal zone lymphoma (pcMZL), pcFCL, and pcDLBCL-LT. Incidence of pcBCL is estimated at 4 per 1,000,000 people per year and increases with age, with pcDLBCL-LT representing only 10-20% of these cases, and pcDLBCL-NOS exceedingly rare.[7,8] pcDLBCL-NOS more often affects men with a mean age in the 60s, as opposed to pcDLBCL-LT with a predilection to women and ages 70 plus. DLBCL itself is the most common lymphoma subtype, accounting for 30-40% of non-Hodgkin lymphomas.[9,10] Most patients present in the 7th decade of life, with increased incidence in men, and often with nodal disease, but 40% of cases primarily present in extra-nodal locations, most often gastrointestinal and then the skin.[11,12]

Clinically, pcDLBCL-NOS often presents as large indurated erythematous plaques or nodules/tumors >5 cm; less commonly the papules/nodules of pcDLBCL-LT.[4] They show a predilection to the trunk, as opposed to pcDLBCL-LT preferentially affecting the lower limbs. pcDLBCL-NOS often present with regional skin involvement of multiple lesions in 1-2 contiguous regions of the body. They often have a more indolent course compared to pcDLBCL-LT, with reports of development of up to 8 years.[4] However, both may rapidly evolve into nodules and tumors and ulcerate.

Histopathological analysis of pcDLBCL-NOS most commonly reveals a diffuse or nodule/diffuse infiltrate predominately of large centroblast cells (>90%) with intermingled medium-sized centrocyte cells and reactive T-cells.[5,6] Extension to the subcutis is frequent, as well as a well-defined Grenz zone, and absence of a dendritic meshwork. Unlike pcDLBCL-LT, effacement of cutaneous adnexa and necrosis are uncommon, and there is a greater degree of reactive T cells, which are usually absent or minimal in pcDLBCL-LT.[6] Immunohistochemical staining reveals strong expression of B-cell markers CD20 and CD79a, and frequently positive staining of BCL6, often without BCL2, which is present in around 90% of pcDLBCL-LT.[4–6,13] Twenty four percent of cases are non-GCB type. MUM1, MYC, and CD10 are variably expressed. Fluorescence in situ hybridization (FISH) testing of MYC, BCL2, and BCL6 rearrangements, amplifications, translocations is encouraged.

Once immunohistopathologic diagnosis of cutaneous DLBCL is made, imaging with PET/CT scan of the chest, abdomen, pelvis, with or without neck and laboratory work up (CBC, CMP, LDH) is recommended to rule out systemic disease and direct management. Bone marrow biopsy should be considered in appropriate patients. Care should be coordinated with hematology and oncology, and often radiation oncology. Although there are no consensus guidelines, pcDLBCL (LT or NOS) is often treated similarly to systemic DLBCL due to their aggressive nature. The chemotherapeutic regimen most often employed is rituximab plus cyclophosphamide, doxorubicin

(hydroxydaunorubicin), vincristine (Oncovin), and prednisone (R-CHOP), with or without field radiation therapy. Local therapy with radiotherapy or surgical excision alone are not commonly recommended due to high rates of relapse, although in the proper setting radiotherapy may be considered for pcDLBCL-NOS due to its less aggressive nature.[5,14] Overall, pcDLBCL-NOS has shown greater response to therapy (81% vs 67%), with less relapses (31% vs 42%), and lower disease related mortality at 5 years (18% vs 50%), compared to pcDLBCL-LT.[6] Further studies into primary cutaneous diffuse large B-cell lymphomas phenotypes and classifications are warranted to aid prognostication and management.

Essential Lesson:

- DLBCL are aggressive mature non-Hodgkin lymphomas that may present primarily on the skin (pcDLBCL-LT/NOS) or secondarily.
- Large erythematous indurated plaques/nodules should raise concern for pcDLBC, especially those associated with nodular development and ulceration.
- Rebiopsy should be obtained if clinical suspicion is high, and/or rash is not resolving.
- Although a disputed entity, pcDLBCL-NOS, or its associated phenotype, may hold prognostic and treatment implications.
- Management involves systemic workup, and coordination of care with hematology/oncology and radiation oncology.

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Case Presented by Jane Zhang, MD,
Timothy Tan, DO, Joan Guitart, MD, Wenhua Liu, MD, and Sheryl Hoyer, MD

History of Present Illness:
A 78-year-old female presented with an itchy rash on her forearm near her left antecubital fossa and on her left abdomen for about two years. It was initially seen and described by her primary care doctor as a red plaque on the left arm. She had minimal improvement with triamcinolone 0.1% ointment twice daily for a few months.

Past Medical History:
Hypertension
Diabetes Mellitus, Type 2

Medications:
Furosemide 20mg daily
Hydrochlorothiazide 25mg daily
Benazepril 40mg daily
Aspirin 81mg daily

Allergies:
No known allergies

Family History:
No family history of skin diseases and autoimmune diseases

Review of Systems:
Negative for fevers, chills, and weight loss

Physical Examination:
General: well-appearing
Dermatologic: left abdomen and left forearm near antecubital fossa each with a poikilodermatous patch; remainder of exam negative for remarkable skin lesions and lymphadenopathy

Laboratory Data / Diagnostic Procedures and Tests:
Histopathology of shave biopsy of the lesion near the left antecubital fossa: the epidermis is infiltrated by numerous atypical lymphocytes composed of predominantly CD3+ T cells. The infiltrate is weakly positive for CD2 and CD5 but appears negative for CD4, CD8, CD7, CD30, granzyme B, and T cell receptor (TCR) gamma/delta. The upper dermis contains mostly mature, reactive lymphohistiocytes.

Complete blood count with differentiation: unremarkable
Lactate Dehydrogenase: normal
Flow cytometric analysis of peripheral blood: no definitive immunophenotypic evidence of an aberrant T-cell population

Diagnosis:
Pagetoid Reticulosis (Woringer-Kolopp Disease)

Treatment and Course:
She was initially treated with clobetasol 0.05% ointment twice daily to affected areas after discussion of treatment options. She later developed a similar lesion of the left forearm distal to the lesion near the antecubital fossa. After several months of treatment, the appearance and pruritus of the lesions improved. She then began using the topical steroid as needed for itch, which was rarely. Regular follow-up was conducted to monitor for disease progression.

Discussion:
Primary cutaneous lymphomas include T cell and B cell neoplasms that present in the skin without any evidence of extracutaneous disease at the time of diagnosis. Cutaneous T cell lymphoma (CTCL) is a group of neoplasms of skin-homing T cells, which in the Western world, makes up about 75 to 80 percent of all primary cutaneous lymphomas[1]. Mycosis fungoides (MF) is the most common type of CTCL, representing approximately 40% of all primary cutaneous lymphomas and 60 percent of all CTCL. The 2018 update to the 2005 World Health Organization-European Organisation for Research and Treatment of Cancer (WHO-EORTC) classification of primary cutaneous T cell lymphomas recognizes only three variants or subtypes of MF with distinctive clinicopathologic features, clinical behavior, and prognosis: folliculotropic MF, granulomatous slack skin, and pagetoid reticulosis[1].

Pagetoid reticulosis also known as Woringer-Kolopp disease is a variant of MF that makes up less than 1% of cases of CTCL[2]. It primarily affects middle-aged adults although the age at diagnosis ranges from 2-89 years; it is slightly more common in males.[3] Patients often present with a slowly progressive, asymptomatic psoriasiform or hyperkeratotic patch or plaque localized to an extremity[3,4]. Less commonly, it may present with multiple lesions or display locally aggressive behavior with a rapid increase in size.[4] Extracutaneous involvement and disease-related deaths have not been reported[2]. Clinical differentials are vast and include eczema, psoriasis, cutaneous tuberculosis, lupus erythematosus, verruca vulgaris, and other neoplastic entities including patch or plaque stage MF.

Histologically, pagetoid reticulosis is defined by a very marked and mostly exclusive intraepidermal proliferation of neoplastic T cells[2]. This infiltrate of highly epidermotropic T lymphocytes occurs in a pattern of pagetoid spread occupying the entire thickness of the epidermis[2]. The atypical cells have medium to large nuclei, sometimes hyperchromatic and cerebriform[2]. Although the superficial dermis may have an inflammatory infiltrate, it consists of mostly small, mature, and reactive lymphocytes; rarely, the upper dermis can contain few neoplastic T cells[2,4]. Immunophenotypically, these atypical cells demonstrate T cell lineage with CD2, CD3, and CD5 positivity[4]. In order of decreasing frequency, atypical cells variably show the following immunophenotypes: CD4-/CD8+, double positive CD4+/CD8+, CD4+/CD8-, or double negative CD4-/CD8-[3]. CD7 is often either aberrantly decreased or completely absent[5]. CD30 expression is variable.[4]

While there is no standard therapy, curative intent treatment with localized radiation or surgical excision is preferred.[2] Radiotherapy demonstrates the highest cure rate and lowest recurrence rate followed by excision[3]. Most cases have complete remission, but infrequent cases of local recurrence or relapse at distant cutaneous sites exist[3,4]. Other treatments that have shown moderate success include: oral or topical bexarotene, photodynamic therapy, phototherapy, nitrogen mustard, topical or intralesional steroids, and imiquimod[3]. Prognosis is very favorable with an overall indolent, benign disease course and a 100% 5-year survival rate. Of note, CD4/CD8 double negative cases have been associated with a higher proliferation index; however, this phenotype does not appear to have prognostic significance[5].

Here, we present a case of the very rare entity of CD4-/CD8- double negative pagetoid reticulosis with an atypical clinical presentation. Since this variant of MF can be a "great imitator" and is often misdiagnosed, a high index of suspicion as well as clinical and histopathologic studies are necessary for accurate and timely diagnosis and treatment.

Essential Lesson:

- Pagetoid reticulosis or Woringer-Kolopp disease is a rare variant of MF that makes up less than 1% of cases of CTCL.
- Histologically, pagetoid reticulosis is defined by a very marked and mostly exclusive intraepidermal proliferation of highly epidermotropic neoplastic T cells in a pattern of pagetoid spread occupying the entire thickness of the epidermis.
- A wide range of clinical presentations exist, and pagetoid reticulosis mimics many skin diseases, making a biopsy critical in helping to make the diagnosis.

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**Case Presented by Yonatan Hirsch, MD,
Wenhua Liu, MD, and Roger Haber, MD**

History of Present Illness:
A 26-year-old female of Native American heritage presented to clinic for evaluation of a diffuse and pruritic rash covering most of her body. The rash began over a year ago and has been spreading over time. She was previously treated for this by her primary care physician who recommended over the counter emollients and low potency topical steroids. The patient also noted asymptomatic lighter patches of skin on her face and trunk, present since early childhood.

Past Medical History:
Asthma, atopic dermatitis, nephrolithiasis, depression, bipolar disorder

Family History:
The patient notes that her mother and brother have been diagnosed with Vogt–Koyanagi–Harada Disease.

Medications:
Hydrocortisone 2.5% ointment

Allergies:
No known allergies

Social History:
Denied tobacco, alcohol or drug use.

Review of Systems:
Endorsed 1 year history of blurry vision and tinnitus in bilateral ears

Physical Examination:
Scattered over the trunk, buttocks, and extremities were many erythematous patches with fine scale and atrophic appearance. Also present were "islands of sparing" of normal and hypopigmented patches of skin. Additionally, there were scattered depigmented patches across the body. There was no observed alopecia or poliosis.

Histopathology:
Skin, Left upper chest, punch biopsy: Atypical lymphocytic infiltrate, with marked fibroplasia and some exocytosis, suspicious for mycosis fungoides. Subsequent molecular PCR studies on sample demonstrated reproducible and predominant PCR product peaks identified by TCR-Beta primers and minor clones by TCR-Gamma primers, confirming diagnosis of mycosis fungoides.

Diagnosis:
Mycosis Fungoides

Treatment and Course:
While biopsy results were pending, the patient was started with triamcinolone 0.1% ointment twice daily. She was also recommended to try phototherapy, but travel restrictions made this difficult. When biopsy results returned, the patient was given Clobetasol 0.05% ointment for thicker lesions. Labs at this time showed a normal serum protein electrophoresis, normal blood flow cytometry and peripheral blood smear negative for Sézary cells. She was referred to oncology for initiation of bexarotene. The patient had not yet visited oncology when she returned to clinic with new erythematous nodules on her right buttock.

Given her known family history of Vogt–Koyanagi–Harada syndrome and the presence of vitiligo on exam as well as ROS complaints of tinnitus and blurry vision, the patient was given referral to genetics, ophthalmology and ENT for further evaluation of a possible Vogt–Koyanagi–Harada syndrome.

Discussion:
Mycosis Fungoides (MF) is a mature T-cell non-Hodgkin lymphoma that represents the most common form of cutaneous T-cell lymphoma (CTCL). Extracutaneous disease involvement is rare and frequently correlates with total body surface area of involved skin. The pathogenesis of this disease is incompletely understood, though alterations in T-cell receptors, JAK-STAT signaling and RNA splicing are believed to be involved. External factors such as environmental chemical exposure and/or infection, specifically with Human T-lymphotropic virus type I (as has been observed in adult T-cell leukemia/lymphoma) have been implicated, though numerous studies have also rejected these as contributing drivers of disease.[2-4] Genetic analyses have demonstrated mutations in tumor-suppressor genes *MLL3* and *TP53* being the most frequent. Additionally, the genes encoding for the tumor necrosis factor receptor 2 protein (TNFR2) are present in 18% of MF patients, resulting in enhanced NF-κB signaling.[5] The neoplastic T-cells in MF are believed to derive from normal skin-homing memory T lymphocytes, which are responsible for skin immunosurveillance. These malignant T cells express surface ligand CCR4, which allows for preferential migration to the skin.[6]

The incidence of all forms of CTCL in the United States is reported to be 6.4 per million persons, with higher rates observed in men and in black patients.[7,8] While primarily a disease that affects older patients, it has been observed in patients younger than 35 years of age, with some cases arising even during the first decade of life. These cases have been associated with unusual forms, including a hypopigmented variant.[9-10] MF is not genetically inherited and first-degree relatives of MF patients do not have a higher risk of developing MF.

The course of MF typically begins with a pre-mycotic period, which can last from months to decades. It is characterized by pruritic, recurring, and non-specific scaling skin lesions. These lesions are often self-limited. The disease will then progress to more persistent skin lesions, with heterogenous morphologies that can include patches, plaques, papules, tumors and generalized erythroderma. 30% of patients with have

patches and plaques limited to <10% of total body surface area while erythroderma will be present in around 15% of cases.[11] There are rarer clinical variants which include bullous/vesicular, ichthyosiform, and/or acral lesions and leonine facies. Cutaneous lesions tend to be pruritic and can negatively impact overall quality of life and psychiatric health. Extracutaneous findings are rare, with the exception of lymph node involvement - this can be seen in around 30% of MF patients.[12]

Given the various morphologies with which MF may present, it is often initially presumed to be other, more common, skin diseases such as psoriasis, eczema, photodermatitis or drug reaction. The diagnosis is often confirmed only after skin biopsy has been performed. A diagnostic point-based algorithm, which utilizes clinical, histopathological, molecular and immunopathologic criteria has been proposed by the International Society for Cutaneous Lymphoma.[13]

On histology, MF demonstrates atypical lymphocytes with cerebriform nuclei infiltrating the dermal-epidermal junction. In early stages of disease, epidermotropism can be seen. Intraepidermal nests of atypical lymphocytes, referred to as “Pautrier's microabscesses”, are pathognomonic for MF. Immunophenotyping is often necessary to confirm diagnosis, with the mature T-cell markers CD2, CD3, CD5, and CD7 routinely tested. The absence of one or more of these markers is suggestive of lymphoma. MF typically expresses CD2, CD3, CD4 and CD5 and lacks expression of CD7 and CD8. In cases of large cell transformation, the expression of CD30 represents a favorable prognostic indicator.[14] Patients suspected of having MF should have a peripheral blood smear performed for the detection of Sézary cells, as an absolute count of 1000 Sézary cells/mm^3 or greater is a diagnostic criterion for Sézary syndrome. The tumor-node-metastasis-blood (TNMB) staging system is used to stage MF, and higher stage disease is associated with worse outcomes requiring more aggressive therapeutic approaches.[15]

Early stage MF (IA – IIA) is characterized by limited skin involvement as well as none to limited nodal involvement with absence of any visceral involvement. Treatment usually consists of topical therapeutics, including corticosteroids, mechlorethamine, retinoids and imiquimod. Localized radiation therapy as well as phototherapy are utilized as well. Advanced stage MF (IIB - IV) often requires the addition of systemic therapies in attempts to limit disease flaring, provide symptom relief and improve survival. Systemic options include low dose methotrexate, systemic retinoids, brentuximab vedotin, mogamulizumab, interferon, PUVA therapy and others. Disease remission has been observed in case reports following allogeneic hematopoietic stem cell transplantation.[16-17]

Vogt-Koyanagi-Harada Disease (VKHD) is a rare, granulomatous, autoimmune disease with multisystem involvement, affecting primarily pigmented tissue such as the eyes, inner ears, meninges, skin and hair.[18] It is seen more frequently in Asian, Middle Eastern, Hispanic and Native American populations.[19] Patients typically present in their second to fifth decade of life and there is a higher incidence among women.[20] The diagnosis is usually clinical and is based on a constellation of findings. These findings

include bilateral chronic iridocyclitis, posterior uveitis, neurologic signs (tinnitus, neck stiffness, CSF pleocytosis) and cutaneous findings (alopecia, poliosis and/or vitiligo). Ocular and neurologic findings tend to precede cutaneous disease manifestations.

The pathogenesis of VHKD is incompletely understood, though the current leading theories postulate a CD4+ T-cell mediated autoimmune response against melanocyte-associated antigens. It is suggested that this response is triggered following viral infection in genetically susceptible patients.[21, 22] Following the trigger, it is believed that T cells target melanocyte specific proteins such as tyrosinase, tyrosinase related proteins and class II major histocompatibility complex.[23] HLA-DR4 has been associated with VKHD as well.[24]

To date, there is no known relationship between VHKD and lymphoma of any sort, though the crucial role of CD4 T cells in both disease processes raises the question of whether similar pathogenesis may be at play. Researchers are already investigating similarities in pathogenesis between CTCL and other T cell mediated inflammatory skin conditions, such as atopic dermatitis and psoriasis.[25] The rates of CTCL are known to be higher amongst patient with these other inflammatory skin diseases, with similar genetic profiles and cytokine signaling pathways. While there are no reports of patients with both MF and VHKD, there is a case report detailing concurrent VKHD and systemic malignant lymphoma in a 69-year-old male.[26]

Essential Lessons:

- MF is the most common subtype of CTCL and can present in various stages with differing morphology, which often delays diagnosis.
- Treatment options depend on disease stage, ranging from topical treatments to stem cell transplant in some cases.
- VKHD represents a rare autoimmune disease targeting pigmented structures, with ocular, cutaneous and neurologic disease findings. While no known relationship exists between CTCL and VKHD, the role of CD4 T-cells in both warrants further investigation into any potential overlap between disease pathophysiology.

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Case Presented by Christine Pak, MD
Sheryl Hoyer, MD, Marylee Braniecki, MD, and Roger Haber, MD

History of Present Illness:
A 39-year-old female presented for evaluation due to ongoing issues with pruritic, occasionally tender, firm papules on her arms and legs that have been present for the last 3-4 years. Patient mentioned that two years ago in Texas, these skin lesions were diagnosed as granulomatous dermatitis, supported by a biopsy. A recent biopsy was undertaken but the results were largely inconclusive.

She had undergone various treatments in the past, including doxycycline, clindamycin lotion, ketoconazole shampoo, metronidazole gel, and a range of topical steroids, but her rashes persisted. Furthermore, the patient started to experience eye-related symptoms about a year ago, including sensitivity to light, redness, and pain. Upon consultations with an ophthalmologist, the patient was diagnosed with panuveitis and referred to a rheumatologist for further evaluation. She was prescribed an empiric course of valacyclovir, methotrexate (15 mg weekly) with leucovorin, a prednisone taper, and multiple ophthalmic solutions. Despite these treatments, she has not experienced any notable improvement in her eye or skin symptoms.

Past Medical History:
Type II diabetes mellitus, hypertension, granulomatous panuveitis, glaucoma, small bowel obstructions, iron deficiency anemia

Medications:
Amlodipine, semaglutide, bimatoprost, brimonidine, dorzolamide-timolol, hydrochlorothiazide, latanoprost, losartan, metformin, omeprazole, prednisolone acetate (ophthalmic solution), prednisone (oral) 60mg/day with slow taper, atorvastatin, cetirizine, ferrous sulfate

Allergies:
No known drug allergies

Social History:
No tobacco, alcohol, or illicit drug use

Family History:
No autoimmune, rheumatologic, or similar cutaneous diseases.

Review of Systems:
The patient endorsed eye pain, worsening vision, and occasional itchiness and tenderness at the site of skin lesions.
The patient denied any fevers, chills, night sweats, unintended weight loss, or joint pains. Patient denied changes in her voice, oral sores, hearing abnormalities, enlarged tonsils, congestion, cough, sore throat, gastrointestinal symptoms, hematuria, bruising, bleeding, or neurologic symptoms.

Physical Examination:
Obesity class 3, Fitzpatrick type 5 female. Face, bilateral extremities, and trunk with diffuse, pink, firm papules and nodules within lichenified, hyperpigmented plaques. Multiple hyperpigmented patches and plaques present on bilateral lower inner thighs and shins. Patient did not have any gross neurological deficits or palpable lymphadenopathy in cervical, supraclavicular, axillary, epitrochlear, inguinal, or femoral regions. Patient did not have palpable hepatosplenomegaly, and the abdomen was soft, nontender, and nondistended. There was no edema.

Laboratory Data/Diagnostic Procedures and Tests:
The following labs were abnormal:
C-reactive protein 9.6 (H); erythrocyte sedimentation rate 28 (H); A1C 10.3 (H); glucose 338 (H); anion gap 13 (H); 25-hydroxyvitamin D 16.3 (L); ferritin 14 (L); RBC 5.66 (H); hemoglobin 10.9 (L); relative lymphocytes 18.9 (H); haptoglobin 496 (H); moderate anisocytes, slight microcytes, slight polychromasia, few ovalocytes, few teardrop cells, few target cells

The following were negative or within normal limits:
Lateral and frontal chest X-ray; QuantiFERON-TB Gold; antinuclear antibodies with reflex; the remainder of the comprehensive metabolic panel; the remainder of the complete blood cell count; HLA-B27; myeloperoxidase antibodies; serine proteinase 3 antibody; toxoplasma IgG; lysozyme; angiotensin converting enzyme; Treponema pallidum IgG; hepatitis B surface antigen; hepatitis C antibody; hepatitis B surface antibody; hepatitis B core IgM; lactate dehydrogenase isoenzymes; varicella zoster virus; herpes simplex virus 1 and 2; cytomegalovirus; human immunodeficiency virus 1 and 2 screening; eye fluid test for fungal, bartonella and mycobacteria; pregnancy test

CT abdomen and pelvis (2017) : Prominent mesenteric lymph nodes in the right lower quadrant tenderness meet size criteria for lymphadenopathy.

PET- CT Imaging (07/2022) : No orbital stranding or abnormal soft tissue metabolic activity to suggest malignancy or active sarcoidosis. Multiple metabolically active soft tissue nodules and stranding in the subcutaneous fat of the infraumbilical anterior abdominal wall and bilateral proximal thighs most likely injection granulomas.

PET- CT Imaging (09/2023) : Multiple ill-defined FDG avid subcutaneous nodules noted diffusely throughout bilateral lower extremities and inferior abdominal wall, consistent with known history of Rosai-Dorfman disease. No FDG avid lymph nodes visualized. FDG uptake within the skin of the chin and tip of the nose with no associated skin thickening or subcutaneous abnormality. Although both places can have physiologic uptake, given patient's condition, disease involvement cannot be excluded.

Histopathology:
Left arm: Folliculocentric xanthomatous histiocytic infiltrate associated with lymphocytes, few plasma cells, and overlying neutrophilic exocytosis

Left leg: Xanthomatous histiocytic infiltrate associated with lymphocytes, neutrophils and plasma cells
In both samples, dense aggregates of large histiocytes with hemophagocytosis were noted. Focal plasma cells and reactive small lymphocytes are present.

Immunohistochemistry: $CD68^+$ and $S\text{-}100^+$ with focal evidence of emperipolesis; $CD1a^-$; $CD79a^+$ plasma cells scattered in the rim of lesion; CD20 and CD3 show a mixture of both B and T cell lymphocytes predominantly at the rim of lesion. Cycline D1 with lesional uptake in both specimens.

Diagnosis:
Rosai-Dorfman Disease (RDD)

Treatment and Course:
After histopathological findings of RDD were noted, the patient was referred to hematology-oncology for evaluation of possible multifocal RDD. Ophthalmology re-evaluated the patient and endorsed that eye findings are consistent with ophthalmic RDD. Patient was resumed on prednisone taper. After hematology-oncology evaluation, the patient underwent a repeat total body PET-CT scan for staging of RDD. The biopsy samples are pending MAPK/ERK pathway mutation testing. Following PET evaluation and genetic testing, she may initiate treatment for a multifocal RDD with MEK inhibitor (Cobimetinib) or conventional therapies (cladribine, cytarabine, or methotrexate)

Discussion:
Rosai-Dorfman disease (RDD) is a rare non-Langerhans cell histiocytic disorder that is characterized by accumulation of abnormal histiocytes in affected tissues. RDD was characterized by Juan Rosai and Ronald Dorfman as “Sinus histiocytosis with massive lymphadenopathy”. Historically, RDD has been considered a benign disorder of unknown etiology with variable outcomes. It is more commonly diagnosed in children and young adults, males, and individuals of African descent. The cutaneous form is more commonly reported in Asian females. The NCCN guidelines for histiocytic neoplasm provided updated recommendations in 2021 for diagnosis and treatment of adults with RDD, and WHO officially recognized RDD as a histiocytic neoplasm in 2022.

Histologically, lesional large histiocytes are $S100^+$, $CD68^+$, and $CD1a^-$, and variable frequency of emperipolesis. Occasionally cyclin D1 may be positive, but this could also be present in concurrent lymphocytic or histiocytic neoplasm. At least one third of RDD cases have gain-of-function mutations in genes of the MAPK/ERK pathway, and there may be opportunities for targeted therapy in patients diagnosed with RDD. Some studies have identified activating mutations of KRAS, NRAS, ARAF and MAP2K1.

In familial RDD, germ line mutations with SLC29A3 have been reported. RDD coexists with an immunologic disease in 10% of cases, such as systemic lupus erythematosus, idiopathic juvenile arthritis, and autoimmune hemolytic anemia. In some cases of extranodal RDDs in the liver/lungs /colon, an increased number of $IgG4^+$ plasma cells were reported.

The classic RDD, also known as nodal RDD, presents with bilateral, massive, and painless cervical lymphadenopathy with or without constitutional symptoms. Other lymph nodes may be involved though less common. Extranodal involvement has been reported in 43% of RDD cases. Cutaneous involvement accounts for 10% of cases, and isolated cutaneous disease is rare. Lesions are typically slowly growing, painless, nonpruritic nodules, papules, and plaques with varying coloration. Any skin site can be involved, and the differential diagnosis at the initial presentation is broad. Other extranodal RDDs can involve hematologic, central nervous system, ophthalmic, head and neck, intrathoracic, retroperitoneal, genitourinary, osseous, gastrointestinal organs. Prognosis correlates with the number of nodal groups and extranodal systems involved by RDD.

The diagnosis and staging of newly diagnosed patients with RDD involve an assessment of disease extent and evaluation for conditions known to coexist with RDD. This would include taking a comprehensive medical history and thorough physical and neurological exam. Some investigators use FDG-PET/CT for initial staging when possible. Routine chest X-ray with neck and abdominal ultrasound are recommended for children and CT of the neck/chest/ abdomen/pelvis is recommended for adults. Laboratory evaluation includes a comprehensive metabolic panel, a complete blood count with differential, reactive markers, quantitative immunoglobulin levels, serologies for HIV, hepatitis panel, uric acid, lactate dehydrogenase, coagulation studies and/or antinuclear antigens and rheumatoid factors.

No uniform approach for treatment has been delineated for RDD given the rarity of the disease. The treatment is best tailored to the individual presentation and clinical circumstances. NCCN guidelines as well as consensus guidelines for RDD suggest that treatment options ranging from observation, surgical debulking, corticosteroid, chemotherapy, immunotherapy, targeted therapy, to radiotherapy may be appropriate.

We present this case of multifocal Rosai-Dorfman disease for clinical interest of a rare disease with extracutaneous findings and comorbidities, expanding our understanding from last month's CDS presentation.

Essential Lesson:

- Rosai-Dorfman Disease is a rare non-Langerhans cell histiocytosis with heterogeneous presentation and prognosis, which is now recognized by WHO as a histiocytic neoplasm since 2022.
- A subset of patients with RDD harbor gene mutations involving MAPK/ERK pathway and targeted such as MEK inhibitor can be considered.
- Patients with extranodal RDD will likely require a multidisciplinary approach and individualized treatment based on their presentation.

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**Case Presented by Lacey Zimmerman, MD,
Michelle Bain, MD and Marylee Braniecki, MD**

History of Present Illness:
A 52-year-old male presented for red to purple discoloration over his right dorsal hand that had been present for 10 years, increasing in size over the last 2 years. He did not have any other similar lesions elsewhere on his body. He endorsed that the lesion first appeared shortly after he had a motor vehicle collision in which he suffered a traumatic brain injury and cervical spine fractures, requiring a C2-C7 cervical spinal fusion surgery.

Past Medical History:
Anxiety, depression, post traumatic stress disorder, migraines, pulmonary embolism, gastroesophageal reflux disease, allergic rhinitis, traumatic brain injury, C2-C7 spinal fusion

Medications:
Aripiprazole, cevimeline, clonazepam, duloxetine, fluticasone, gabapentin, mirtazapine, pantoprazole

Allergies:
Latex

Social History:
Former smoker <2 pack years

Review of Systems:
Denied weight loss, headaches, muscle weakness, numbness or tingling of R hand

Physical Examination:
Violaceous plaque on R dorsal hand, overlying the 4^{th} and 5^{th} metacarpal heads

Histopathology:
4mm punch biopsy revealed increased thin-walled vasculature in the upper dermis

Diagnosis:
Acquired, trauma-induced port-wine stain, or Fegeler syndrome

Treatment and Course:
Pulse dye laser therapy was recommended, but the lesion continued to increase in size. He was then referred to orthopedic surgery, and an MRI revealed dilated, entangled vascular structures at the dorsal aspect of the right hand near the 4^{th} and 5^{th} metacarpal heads. This was suspicious for an arteriovenous malformation (AVM), which was surgically resected and confirmed on pathology.

Discussion:

Fegeler syndrome, or trauma-induced port-wine stain, was named after the physician who first described the condition in 1949 after an adult patient suffered a head injury and developed a port-wine stain on his face following the first branch of the trigeminal nerve. Less than 100 cases of trauma-induced port-wine stain have been documented since it was first described. As the name implies, it is believed that these acquired port-wine stains develop secondary to trauma; however, there are differences in the literature regarding the type of trauma. Some cases cite incidences of acquired port-wine stains occurring in the areas directly impacted, while others describe occurrences of injury to the brain or spinal cord leading to port-wine stains at a distant site. Acquired port-wine stains following frostbite injury, isotretinoin, herpes zoster infection, spinal root compression, and brain tumor have been reported, among others.

The morphology and histology of trauma-induced port-wine stains are indistinguishable from congenital port-wine stains. On exam they usually initially appear as pink to red macules to patches that thicken and darken over time, some developing nodules and deep violaceous color. On histology, proliferated, dilated capillaries in the dermis are seen. Capillaries are identified by their single layer of endothelial cells. While port-wines stains are considered capillary malformations, as they evolve with time, so do their pathological features. Nodules that develop within port-wines stains have been found to be other vascular malformations, including AVMs, as seen in our patient.

Two main theories exist regarding the pathophysiology of the acquired port-wine stains. Decreased perivascular nerve density within port-wine stains has been demonstrated, which led to the hypothesis that trauma may cause damage to sympathetic neural modulation of vascular tone and therefore ectasia, or dilation, of capillaries. The other theory is that trauma may cause perivascular atrophy, which decreases vessel support and can lead to vessel ectasia.

The patient presented may have developed his port-wine stain secondary to trauma directly to his hand or to his central nervous system. It is notable that the area of skin affected aligns with a dermatome that could have been impacted based on the location of his neck injury and spinal fusion surgery. A dermatome is a section of skin that is supplied and innervated by one nerve root. Therefore, in theory, injury to the nerve root in the neck could have impacted the sympathetic neural modulation of vascular tone in the hand.

While port-wine stains are benign, they can affect patients' quality of life and patients may desire treatment. As with congenital port-wine stains, first line treatment is with pulsed-dye laser therapy (PDL). Other laser therapies including intense pulsed light (IPL), potassium-titanyl-phosphate (KTP), and long-pulsed Nd:YAG have also been used to treat port-wine stains. Unfortunately, port-wine stains may re-darken after laser therapy and retreatment may be desired. In the past, electrotherapy, cryotherapy, cosmetic tattooing, and skin grafting were other therapies used. Novel therapies currently being investigated include the use of topical antiangiogenic medications with laser therapy (laser-assisted drug delivery) and photodynamic therapy (PDT) employing a photosensitizer designed to specifically target vessels.

Essential Lesson:

- Port-wine stains can be acquired secondary to trauma, also known as Fegeler syndrome.
- Trauma-induced port wine stains have been hypothesized to be secondary to perivascular atrophy and/or damage to neural modulation of vascular tone.

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**Case Presented by Ryan Bunney, MD,
Marylee Braniecki, MD and Roger Haber, MD**

History of Present Illness:
A 62-year-old male presented for evaluation of solid facial edema present for the past 7 years. The patient reported his facial swelling was most severe in the morning and by the afternoon, he sometimes had difficulty opening his eyes due to the swelling. This severely impacted his quality of life. He had previously followed with ophthalmology, oculoplastic surgery, otolaryngology, and allergy and immunology who had found no clear pathology despite extensive workup with MRI, MRA, and CT imaging. The most recent CT scan of the sinuses was unremarkable, apart from cutaneous and subcutaneous thickening of the right inferior tarsus. He also reported intermittent facial erythema with no known triggers. Review of systems and his past medical history were otherwise unremarkable.

The patient had last been seen in a dermatology clinic 3 years prior for the same complaint. At that time, right cheek punch biopsy showed perivascular and perifollicular chronic inflammation, dermal edema, superficial granulomatous inflammation, and focal deep dermal calcification. His facial swelling was attributed to severe rosacea. He was treated with doxycycline, pentoxifylline, diphenhydramine, topical econazole, and dietary modification without any significant improvement. The patient subsequently completed 8 months of oral isotretinoin therapy without significant improvement. The only treatment he received that had temporarily improved his symptoms was a 5-day course of oral corticosteroids.

Past Medical History:
Allergic rhinitis

Past Surgical History:
None

Medications:
Cetirizine 10mg daily seasonally

Allergies:
Seasonal
Naproxen
Sulfa Antibiotics

Family History:
No family history of skin conditions or autoimmune conditions.

Review of Systems:
Blurry vision. No fevers or chills.

Physical Examination:
Right side of the face from the forehead to the nasolabial fold showed non-pitting, nontender edema and a woody, smooth-surfaced, non-scaling induration. Poorly demarcated erythema is present on the nose and bilateral cheeks.

Laboratory Data/ Diagnostic Procedures and Tests:
Elevated: ESR 31

Normal/negative: CBC with differential, CMP, C-1 esterase inhibitor, C3, C4, Tryptase, CRP, ANA, anti-SS-A Ab, anti-SS-B Ab, anti-smith Ab, anti-ribonucleoprotein antibody, IgG, IgA, IgM, serum protein electrophoresis, urinalysis

Histopathology:
Right cheek, skin: Small solitary facial osteoma cutis with adjacent microfocal, multinucleated giant cell and perifollicular granulomatous reaction, superficial capillary ectasia, chronic perifolliculitis, and Demodex folliculorum

Diagnosis:
Morbihan Disease

Treatment and Course:
The patient was started on oral ivermectin 200 mcg/kg weekly (weight: 28.24 kg) for a total of 6 doses as well as 1% topical ivermectin twice daily. At his follow up visit one month later, the patient's facial swelling, as well as overall quality of life had improved significantly. Treatment with a repeat course of isotretinoin was discussed at the initial visit but was deferred at this time given clinical improvement. The patient continued topical ivermectin treatment twice daily.

Discussion:
The mean age of Morbihan Disease (MD) diagnosis is estimated at 49 years old with a 2:1 predilection for males. It most commonly involves the central face, which includes the eyelids, periorbital region, glabella, nose, cheeks, and malar region. While MD is considered a rare variant of acne rosacea, it is unclear whether patients must demonstrate clear rosacea manifestations to develop MD. Clinical manifestations of MD are thought to be caused by local imbalance in lymphatic production and drainage. It is postulated that inflammation destroys collagen and elastic fibers supporting connective tissue around dermal lymphatic and blood vessels. This ultimately results in increased vessel permeability seen in chronic rosacea, acne, or contact dermatitis. Chronically, permanent local dysregulation of lymphatic vessels and lymphatic obstruction by granulomas and histiocytes may result in lymphedema. The histopathologic features of MD present on biopsy include dermal edema, dilation of blood vessels, sebaceous hyperplasia, perivascular inflammatory infiltrate and fibrosis, and granulomatous reaction with more than one-third of cases showing dilated lymphatic vessels. Recent studies have implicated increased D2-40 expression, a lymphatic endothelial marker found in the skin’s endothelial cells that promotes expansion of lymphatic vessels, suggesting that lymphangiogenesis may be involved in the pathogenesis of MD.

A recent systematic review found that among patients who were able to achieve complete response to treatment without disease recurrence, 35% of patients underwent treatment with isotretinoin, 22% were treated with tetracycline antibiotics, 22% underwent surgical intervention, and 7% were treated with intralesional steroid injections. Among treatments, isotretinoin therapy is considered first line. In our patient, biopsy revealed granulomatous inflammation, demodicosis, and dilation of capillaries, consistent with typical findings of MD. He had seen no improvement in symptoms despite receiving treatment with isotretinoin and doxycycline. However, he had previously experienced improvement with corticosteroid therapy and after only one dose of ivermectin.

Ivermectin is a broad-spectrum antimicrobial drug used to treat helminth, bacterial, and viral infections and has shown to hold anti-inflammatory and anti-carcinogenic properties as well. Its anti-inflammatory action is thought to result from inhibition of cytokine production by macrophages, blockade of activation of NF-kB, and inhibition of toll-like receptor 4 (TLR-4) signaling. In rosacea, ivermectin primarily acts as an anti-inflammatory and anti-parasitic agent targeting *Demodex* mites, as seen in our patient. Ivermectin has been shown to be more effective for MD than metronidazole with a favorable side effect profile.

This case of treatment-resistant Morbihan disease responsive to ivermectin therapy highlights the recalcitrant nature of MD that is often unresponsive to first line oral isotretinoin. In these patients, alternative therapies such as ivermectin are promising alternatives.

Essential Lessons:

- Morbihan Disease is thought to be due to a local imbalance in lymphatic production and drainage.
- There are no biochemical or histopathological findings specific to Morbihan Disease and the differential diagnosis is wide and varied, rendering diagnosis and treatment of this disease especially challenging.
- Isotretinoin is considered a first line treatment, however, due to the recalcitrant nature of this disease, alternative therapies may need to be considered.
- Oral ivermectin is a promising treatment due to its anti-inflammatory effects and anti-parasitic actions against *Demodex* mites.

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**Case Presented by Allison Ellis, MD PhD,
Marylee Braniecki, MD and Maria Tsoukas, MD PhD**

History of Present Illness:
Patient is a 61-year-old male presenting with a right cheek lesion for three months. Patient stated he first noticed the lesion a few months ago, at the time of his renal cell carcinoma diagnosis. He denies any similar lesions in the past. He denies any personal or family history of skin cancer.

Past Medical History:
Renal Cell Carcinoma Stage IV with metastasis to bone and lung (1/24/23)
Myocardial Infarction (2020)
Hypertension

Medications:
Axitinib 5mg PO BID
Pembrolizumab
Zometa
Atorvastatin 80mg PO QHS
Famotidine 20mg PO BID
Ferrous Sulfate 325mg PO QD
Metoprolol Succinate 12.5mg PO QD

Allergies:
No Known Drug Allergies

Social History:
Former smoker
Former alcohol use

Review of Systems:
On review of systems, he reported associated bleeding but denied any facial pain.

Physical Examination:
Skin exam was significant for a 0.8 cm x 1.3 cm red dome-shaped, well-circumscribed nodule with central hemorrhagic crust over the right malar cheek.

Laboratory Data/Diagnostic Procedures and Tests:
Not applicable

Histopathology:
Skin, right cheek; Clear cell carcinoma consistent with metastatic renal cell carcinoma

Diagnosis:
Metastatic Renal Cell Carcinoma to Cheek

Treatment and Course:
Patient continued on the current treatment plan per hematology/oncology team at Mount Sinai. No further dermatological work-up was deemed necessary at this time.

Discussion:
Renal Cell Carcinoma (RCC) is the most common type of primary neoplasm to affect the renal system and accounts for about 2-3% of all solid tumor cancers (1). There are multiple known subtypes of RCC, with clear cell being the most common, accounting for approximately 75% of all RCC cases (2). While the exact pathophysiology of RCC development and progression is unknown, diagnosis of RCC has been associated with advanced age, being of the male sex, deletion of chromosome 3p (specially for the clear cell variant), and various genetic diseases such as Von Hippel Lindau (VHL) and Tuberous Sclerosis (TSC) (1,3,4).

In about 30% of cases, metastasis to distant organ sites is present upon the initial diagnosis of RCC (5,6). The most common sites for RCC metastasis are the lung, liver, and bone (5,6). Skin has been documented as the seventh most common site for RCC metastasis (7). Numerous reports have been published describing cutaneous RCC (8-10). Per these case reports, diagnosis of metastatic RCC to the skin typically occurs months to years after the primary diagnosis of RCC has been made. However, in about 10-20% of patients, the skin lesion is the first sign of underlying RCC (10,11).

Metastatic RCC to skin has been frequently described as a rapidly growing, flesh colored to red-purple nodule (10,12). Clinically, cutaneous RCC may appear similar to hemangioma, basal cell carcinoma, or pyogenic granuloma (10,13). Due to its potential to mimic other dermatological conditions, it is imperative that proper diagnosis is made with a skin biopsy (13). Histological markers for RCC, specifically cutaneous RCC, include CD-10, renal cell carcinoma marker, epithelioid membrane antigen, and carcinoembryonic antigen (14).

Treatment of cutaneous RCC is carried out by a multidisciplinary team involving oncologists, dermatologists, and urologist. The majority of treatment is typically carried out by the primary oncology team. Following patient risk stratification, treatment for stage IV, metastatic RCC typically involves nephrectomy with immune checkpoint inhibitor-based combination therapies (IBC) (15). From a dermatological standpoint, treatment consists of local excision/ metastasectomy followed by frequent surveillance to assess for disease recurrence (10).

Essential Lesson:
- In about 10-20% of patients with metastatic RCC to skin, the dermatological findings are the first sign or symptom of underlying disease.
- As metastatic RCC can mimic many common, benign dermatological disorders, biopsy is imperative to make the correct diagnosis.
- Following lesion excision, frequent dermatological exams should be carried out to assess for any disease recurrence.

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