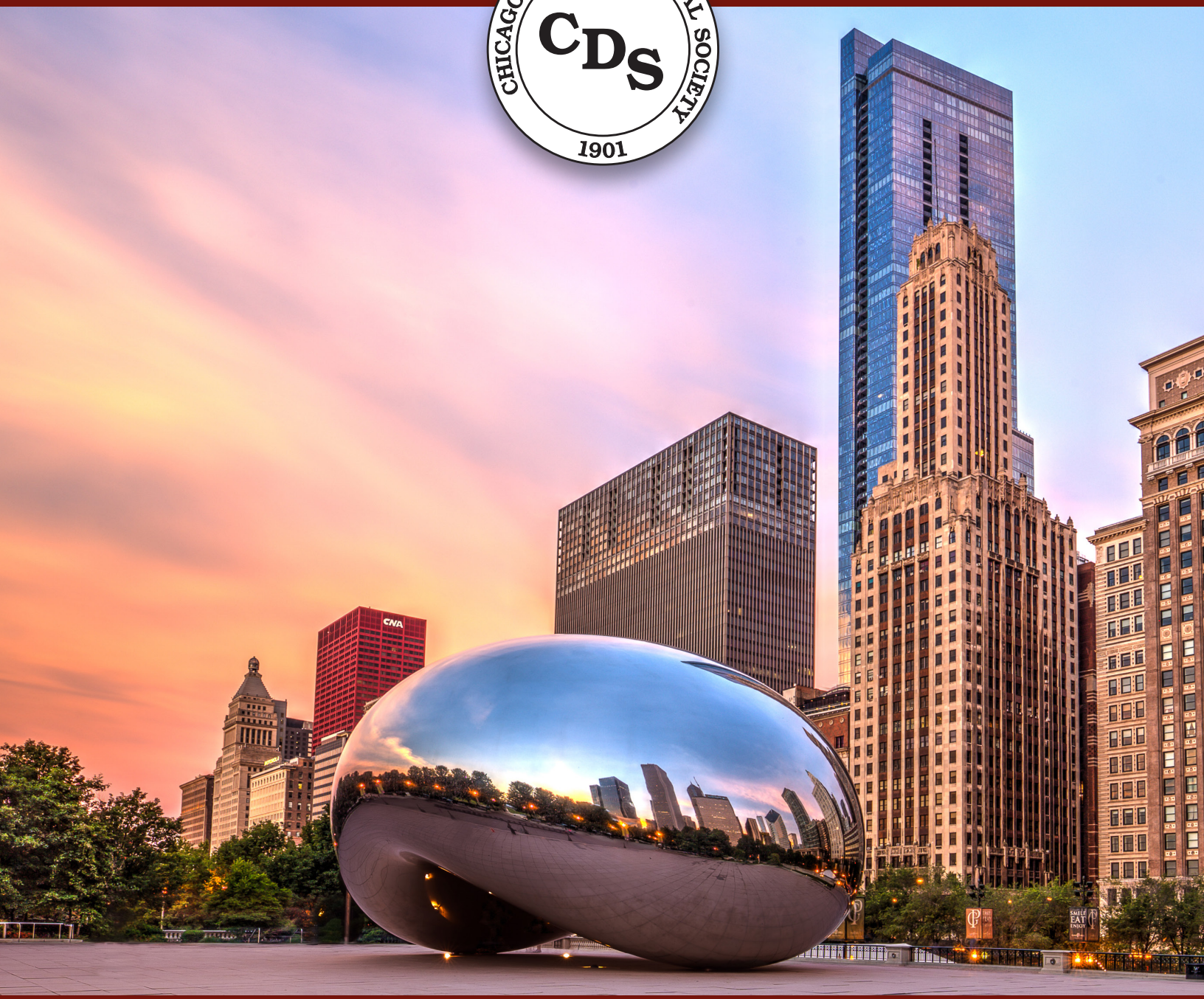
PROTOCOL BOOK • OCTOBER 9, 2024

CHICAGO DERMATOLOGICAL SOCIETY

Monthly Meeting

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



Chicago Dermatological Society

PROTOCOL BOOK
October 9, 2024

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

Guest Speaker: **Brian Simmons, MD**
Assistant Professor of Dermatology at Dartmouth-Hitchcock
Director of Clinical Trials
Director of Social Media and Website

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INVITED GUEST LECTURER

Brian Simmons, MD

Throughout my professional career I have had the unique opportunity to build a strong science background from basic science, translational research, and experience in clinical dermatology. My research in dermatology is broad including: disorders of hair and nails, inflammatory dermatosis, pediatric dermatology, continuing medical education and the humanistic side of medicine. I have published over 50 papers, and written multiple book chapters in the field of dermatology in high impact journals such including: Journal of Investigative Dermatology, JAMA Dermatology and Journal of the European Academy of Dermatology. Currently I am an Assistant Professor of Dermatology at Dartmouth-Hitchcock, the Director of Clinical Trials and the Director of Social Media and Website.

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PROGRAM

Co-hosted by
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October 9, 2024
Gleacher Conference 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** *Claudia Hernandez, MD - CDS President*
9:00 a.m. - 10:00 a.m.	**Morning Lecture: Complex Medical Dermatology: Interesting Cases from the Upper Valley** *Brian Simmons, 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: Updates in Pyoderma Gangrenosum(PG)** *Brian Simmons, MD*
2:00 p.m.	**Program adjourns**

University of Illinois at Chicago
Department of Dermatology

Chicago Dermatological Society Meeting
October 9, 2024

Dermatology Residents

Fourth Year
Ryan Bunney
Jane Zhang
Christine Pak
Samantha Hunt

Third Year
Alex Woods
Allison Ellis
Yoni Hirsch
Lacey Zimmerman

Second Year
Francisco Padron
Joshua Burshtein
Melissa Nickles
Sheena Chatrath

TABLE OF CONTENTS

Resident Case Presentations & Discussion

Case 1 presented by Melissa Nickles, MD, Ryan Bunney, MD, and Roger Haber, MD

History of Present Illness:
A 28-year-old female presented for evaluation of yellow-orange discoloration of the face and bilateral hands and feet. She reported that the discoloration had been present for six years and was asymptomatic. She consumed a healthy diet consisting of numerous vegetables and specifically reported high carrot and broccoli intake over the last few years.

Past Medical History:
Irregular periods, Hirsutism, Acne

Medications:
None

Allergies:
Penicillin - anaphylactic reaction and rash

Family History:
Yellow skin discoloration in both her mother and sister
Hashimoto's disease in her mother and maternal grandmother
Cirrhosis in her maternal grandmother

Review of Systems:
Negative

Physical Examination:
Her exam was significant for diffuse yellow-orange discoloration of the face and bilateral hands and feet. The discoloration was greatest on the palms and soles and notably spared the sclera and mucous membranes.

Laboratory Data:
Elevated: Carotene level 532 (reference range 60-200)

Normal: CBC, CMP, bilirubin, Vitamin A levels, copper levels, cortisol levels, hepatitis panel, alpha-1 antitrypsin, urinalysis, and TSH

Diagnosis:
Carotenemia

Treatment and Course:
The patient was advised to reduce her intake of high-carotene foods (carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli, etc.). We suspect that her skin pigmentation will return to normal with dietary modification.

Discussion:
Carotenemia describes yellow pigmentation of the skin secondary to increased blood-carotene levels.[1] This condition most commonly presents in infants and toddlers who consume large amounts of carrots in commercial infant food combinations.[2] Cooking, pureeing, or mashing vegetables breaks down their cell wall and increases carotene availability for absorption, further making infants more

susceptible to this condition.[3] However, carotenemia can also be seen in older children and adults, particularly those who follow a vegetarian diet and eat large quantities of carotene-rich fruits and vegetables.[4] A high level of carotene is found in certain fruits and vegetables. Fruits include apricot, cantaloupe, mango, orange, papaya, peaches and prunes. Vegetables include carrots, green beans, asparagus, broccoli, cucumber, lettuce, parsley, spinach, squash, mustard, pumpkins, kale, and sweet potatoes.[3] While some carotene gets converted to vitamin A in the duodenum during digestion, the process of conversion is very slow and massive quantities of carotene consumption cannot cause vitamin A toxicity.[3]

Carotene is a yellowish lipochrome that is normally present in keratin.[3] The stratum corneum of the skin has a high lipid content and affinity for carotene; therefore, the yellow discoloration is usually most prominent on the palms and soles due to the thickness of the stratum corneum in those areas.[3] Notably carotenemia spares the sclera of the eyes and mucous membranes.[3] This is an important distinction to make to differentiate carotenemia from jaundice due to elevated bilirubin levels. Accurately differentiating between these conditions can avoid unnecessary workups and referrals. A similar condition to carotenemia, lycopenemia, has also been described.[3] Lycopene is an isomer of beta-carotene found in tomatoes and other fruits.[5] Elevated levels of blood lycopene from ingesting high quantities of tomatoes or tomato juice can cause a deep orange pigmentation of the skin, similar to carotenemia.[3]

Carotenemia is a benign condition and the diagnosis can be made clinically. It can be seen with excessive ingestion of carotene (greater than 30mg a day) for a prolonged period.[6] This is roughly equivalent to eight medium-sized raw carrots, 16 ounces of carrot juice, or one and a half cups of cooked sweet potato per day.[7–9] Carotene levels can be checked and typically exceed 250 μg/dl in affected patients.[3] With dietary modification, skin pigmentation should return to normal in two to six weeks.[3] Although it may be delayed several months after carotene levels return to normal due to the lipophilic nature of carotenoids.[10] Carotenemia has also been associated with hypothyroidism and diabetes mellitus in the literature.[3,11,12] This is likely due to an increase in beta-lipoproteins seen in these conditions, with subsequent decrease in the conversion of carotene into vitamin A.[3] The condition has also been associated with anorexia nervosa in patients who consume a pure or predominantly vegetarian diet.[4] Therefore, if clinical suspicion is present, it may be reasonable to check for these comorbid conditions in a patient presenting with carotenemia. Metabolic carotenemia due to a deficiency of the beta-carotene 15-15' dioxygenase enzyme, which converts carotene into Vitamin A, has also been described in familial cases.[13] The mode of inheritance is unknown and has been described in individuals exhibiting carotenemia in the absence of excessive carotene intake.[14,15] A referral to genetic counseling may be considered in such cases. While our patient's positive family history of carotenemia does raise suspicion for a genetic defect in carotene metabolism, we suspect that her positive family history is more likely due to similar dietary habits among herself and her family members.

Essential Lessons:

- Carotenemia is a benign condition characterized by yellowish discoloration of the skin. It is diagnosed clinically and can be reversed with dietary modification.
- The absence of scleral and mucosal involvement differentiates carotenemia from jaundice.

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Case 2 presented by Francisco Padron, MD, Marylee Braniecki, MD, Michelle Bain, MD

History of Present Illness:
A 12-year-old female presented with a several-week history of an asymptomatic truncal rash. Approximately two months after the initial onset, the rash became painful, leading the patient to seek medical attention at an urgent care facility. She was diagnosed with herpes zoster (shingles) and initiated on a 10-day course of antiviral therapy, the specific agent of which was not documented. In addition, she was prescribed triamcinolone cream for topical application, which she used once daily.

Past Medical History:
Asthma, Migraines without aura

Medications:
Acetaminophen, Albuterol, Fluticasone furoate, Ibuprofen, Loratadine

Allergies:
No known drug allergies

Review of Systems:
Endorsed pain associated with the rash

Physical Examination:
On physical examination of the left trunk, there were numerous tiny pink papules coalescing into a linear plaque with an overlying white scale along a line of Blaschko. Superiorly, a few papules and linear plaques were seen in a similar distribution.

Histopathology:
Skin, lower back. Mild psoriasiform epidermal hyperplasia with alternating orthokeratosis and parakeratosis, minimal spongiosis and patchy hypogranulosis.

Diagnosis:
Inflammatory linear verrucous epidermal nevus (ILVEN)

Treatment and Course:
The patient was initially started on triamcinolone 0.1% ointment, applied twice daily, pending biopsy results. The patient continued this treatment once the diagnosis of ILVEN was confirmed. Upon follow-up one month later, the patient reported minimal improvement in the appearance of the rash and worsening pruritus. During this visit, the patient also noted an asymptomatic linear rash on the left palm that had been present before the onset of the truncal rash. In addition to triamcinolone, the patient tried and failed topical clobetasol and fluocinonide.

Due to the lack of significant improvement with topical steroids and persistent pain accompanied by pruritus, the patient was referred for laser therapy. Treatment involved the use of a combination of KTP 523nm laser and Nd:YAG 1064nm laser. At the follow-up visit one month later, the lesion had enlarged and exhibited a more verrucous appearance. Given the failure of both topical steroids and laser therapy, the patient was started on calcipotriene ointment, applied once daily to the affected areas. The patient was also referred to an expert in laser therapy for further evaluation and consideration of additional therapy options. The patient has been urged to pursue genetics evaluation to guide potential targeted therapy.

Discussion:

Inflammatory Linear Verrucous Epidermal Nevus (ILVEN) is a rare cutaneous disorder that typically manifests in early childhood and follows a chronic, often refractory course.[1] The condition is characterized by the development of erythematous, scaly, and verrucous plaques arranged in a linear pattern, most commonly along the lines of Blaschko.[2] These lines represent pathways of embryonic skin cell migration, suggesting that ILVEN results from genetic mosaicism, where postzygotic mutations occur in a subset of keratinocytes during development.[2,3] The lesions are predominantly unilateral and frequently involve the lower extremities, though cases with involvement of the trunk, arms, and face have been documented.[1]

Clinically, ILVEN is distinguished from other epidermal nevi by its persistent pruritus and inflammation. The pruritus associated with ILVEN is often severe and contributes significantly to the patient's discomfort and reduced quality of life.[1] Histopathologically, ILVEN shares similarities with psoriasis, exhibiting features such as parakeratosis, acanthosis, and an inflammatory infiltrate in the dermis.[4,5] This resemblance has historically led to the hypothesis that ILVEN may represent a mosaic form of psoriasis or a related inflammatory dermatosis.[4] However, the distinct linear distribution and early onset of ILVEN help differentiate it from other conditions in the differential diagnosis, such as linear lichen planus and verrucous epidermal nevus.[1,4] Additionally, advancements in genotyping have established ILVEN as a genetically distinct entity driven by postzygotic mutations resulting in genetic mosaicism as well as from germline X-linked variants.[6] Multiple causative genetic variants have been identified, including mutations in GJA1, ABCA12, CARD14, PMVK, NSDHL, HRAS, and KRT10.[7] These discoveries underscore the genetic basis underlying ILVEN's pathogenesis.

Management of ILVEN poses a considerable challenge due to its recalcitrant nature. First-line treatments typically include topical corticosteroids and keratolytics, which may provide temporary relief from pruritus but often fail to achieve significant or sustained improvement in the appearance of the lesions.[1] Other topical agents, such as calcineurin inhibitors and retinoids, have been employed with varying degrees of success.[6,8] In recalcitrant cases, systemic therapies or physical modalities such as laser therapy (including CO2 laser and pulsed dye laser) and cryotherapy have been explored.[9,10] The identification of various genetic mutations underlying ILVEN has facilitated the development of targeted therapies aimed at specific cellular modulators. One pediatric patient with treatment resistant ILVEN demonstrated elevated levels of IL-12 and IL-23 on testing. The patient exhibited a marked and sustained improvement with ustekinumab therapy.[11] Similar outcomes have been replicated using secukinumab in ILVEN patients harboring CARD14 mutations.[12] Comparable therapeutic efficacy has been observed in ILVEN patients with associated mutations in NSDHL, a gene involved in cholesterol biosynthesis. These patients have responded favorably to topical cholesterol/simvastatin treatment.[7] Despite these multimodal interventions, recurrence is common, and the lesions may persist into adulthood, underscoring the need for more effective therapeutic strategies including genetics evaluation for purposes of targeting therapy.

Essential Lessons:

- ILVEN is a rare, chronic condition that usually presents in childhood with persistent pruritic and verrucous lesions
- ILVEN often mimics psoriasis histologically, therefor requiring careful differentiation based on clinical presentation and genetics evaluation.
- ILVEN is often refractory to conventional treatments. Employing targeted therapies based on mutational profiles has shown some success.

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Case 3 presented by Sheena Chatrath, MD, Ola Bode Omoleye, MD, Sheryl Hoyer, MD

History of Present Illness
A 31-year-old male presented to dermatology with pink papules and plaques on the right anterior thigh and right antecubital fossa. The patient denied pruritus, pain, or drainage of the lesions. He noted the lesions first appeared on his arm two years prior to his appointment, while the lesion on the leg appeared only a few months prior. He denied any history of skin conditions, however, noted a history of sensitive skin that worsened during the winter.

Past Medical History:
Hypertriglyceridemia, Allergic rhinitis, Primary open angle glaucoma, Obstructive sleep apnea

Medications:
Latanoprost 0.024% solution, Fluocinonide 0.05% ointment

Allergies:
No known drug allergies

Family History:
Glaucoma, Rheumatoid Arthritis, Hypertension

Physical Examination:
On physical examination of the right antecubital fossa, there were well circumscribed, pink papules coalescing into plaques. On the anterior right thigh, there was a well-circumscribed pink plaque with minimal overlying scale.

Histopathology:
Skin, right arm and thigh, H&E: Clonal Kappa-Restricted Plasma Cell Neoplasm
Histologic sections showed variably diffuse and nodular aggregates of plasma cells involving the dermis and subcutaneous tissue admixed with mature appearing lymphocytes. The plasma cells were predominantly mature with rare atypia demonstrated by bi-nucleation. Immunohistochemical stains showed the plasma cells were positive for MUM-1 and IgG with a clonal kappa restriction by in-situ hybridization (lambda negative).

Labs and Imaging:
CBC, CMP, SPEP, SIFE, UPEP, IgG, IgA, IgM, sFLC, Beta2 Microglobulin, LDH, VEGF, PET CT scan, and bone marrow biopsy were performed and unremarkable

Diagnosis:
Primary cutaneous plasmacytoma

Treatment and Course:
Our patient was initially treated with topical steroids. However, after a confirmed biopsy of a plasma cell neoplasm and negative work up for multiple myeloma, he was referred to radiation oncology for localized radiation to the affected areas of the arm and thigh. He will also follow with oncology every three months for repeat multiple myeloma lab work, given risk for these lesions to progress to multiple myeloma. He will be seen by dermatology once yearly for a full body skin examination.

Discussion:

Plasmacytomas are plasma cell neoplasms without underlying systemic disease. They are divided into two classifications, solitary plasmacytoma of bone (SBP) and extramedullary plasmacytoma (EMP), with EMP arising outside of the bone marrow[1]. While EMP most commonly affects the upper respiratory tract, in rare cases it originates in the skin and is known as primary cutaneous plasmacytoma (PCP).[2]

PCP is a subtype of marginal B-cell lymphoma, consisting of plasma cells localized to the skin without underlying multiple myeloma (MM).[2,3] It has been reported that PCP represents only 6% of all plasma cell malignancies, and is more common in adult males aged 55-60 years and African American patients.[1] PCPs are categorized into solitary cutaneous plasmacytomas and multiple cutaneous plasmacytomas, with multiple lesions reported to have higher likelihood of progression to multiple myeloma and death compared to solitary lesions.[1,4] Lesions typically appear as nonulcerated, dermal, purple-red plaques, and can present anywhere on the body.[1,4] While the pathophysiology is not well understood, it is thought that elevated IL-6 as well as abnormalities in chromosomes 1, 9, 13, 14, and 19, play a prominent role in tumorigenesis. Additionally, other studies have reported an increased expression of stromal cell-derived factor 1 (SDF-1) in plasmacytomas, a chemokine known to increase cellular proliferation. [1,5]

In patients suspected to have a plasmacytoma, it is important to distinguish PCP from secondary cutaneous plasmacytoma due to underlying multiple myeloma. Skin biopsy of PCP typically illustrates a diffuse dermal or subcutaneous infiltrate of monoclonal plasma cells with or without the presence of a Grenz zone.[1,6] Immunohistochemical studies may show positive staining for CD138, CD38, and MUM-1 markers.[1,6,7] If skin biopsy is concerning for a plasma cell neoplasm, urgent referral to hematology-oncology services is warranted to rule out multiple myeloma. The workup for MM includes CBC, CMP, SPEP, UPEP, SIFE, LDH, Beta-2 Microglobulin, UIFE, PET CT, and bone marrow aspirate with FISH to evaluate immunoglobulin patterns as well as neoplastic involvement of the bone or bone marrow. In addition to laboratory work up and imaging, at least one of the CRAB criteria (hypercalcemia, renal insufficiency, anemia, or osteolytic bone lesions) is required to make the diagnosis of MM.[1]

Treatment of plasmacytomas includes radiotherapy, surgery, or chemotherapy, and is dependent on the severity of disease.[1] Previous studies have illustrated that EMPs typically resolve with local therapy alone, with single lesions having better outcomes than multiple lesions.[4,8] Local therapy is often curative, however, 14-20% of patients may have recurrence of disease, while some patients may have metastatic spread to the lymphatic system after treatment.[4,9]

Given the occurrence of plasmacytomas are rare, prognosis is not well studied. In one population-based study of 1676 patients with EMP, patients that were male, aged 65 years or older, or of African American race, were at increased risk of death in comparison to other patient demographics.[9] In another systematic review of 66 patients, those with treated solitary lesions were less likely to have recurrence of disease, and more likely to survive than those with multiple lesions.[4] There is conflicting literature regarding the optimal treatment option for patients with EMP. While radiation is the most common treatment, some studies have suggested that surgical removal or surgical removal in addition to radiation, have resulted in improved long-term outcomes compared to radiation alone. Long term outcomes with systemic therapy have not been well studied, however, one study did not find a significant improvement in survival.[9] Further studies are needed to evaluate the efficacy of each of these therapies as well as the combination of therapies in overall survival, disease recurrence, and metastases of disease.

We describe this case of multiple primary cutaneous plasmacytomas to highlight the occurrence of a rare plasma cell neoplasm, that if left untreated can progress to multiple myeloma. Early recognition and management of this condition can result in less invasive treatment options for patients and improve long term outcomes.

Essential Lessons:

- Patients with confirmed cutaneous plasmacytomas should have immediate evaluation with hematology-oncology to distinguish between PCP and secondary cutaneous plasmacytoma due to multiple myeloma.
- While most patients with PCP can be treated with local radiation therapy, consider surgical removal alone/or in addition to radiation, particularly in those with greater disease burden.
- After treatment, consider monitoring regularly with blood work in addition to yearly full body skin exams to evaluate for recurrence of disease or progression to MM.

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Case 4 presented by Yonatan Hirsch, MD, Ola Bode Omoleye, MD, Roger Haber, MD, and Maria Tsoukas, MD, PhD

Patient 1:

History of Present Illness:

A 43-year-old female with hypertension, stage IV chronic kidney disease, nephrotic syndrome secondary to AA amyloidosis and polysubstance use had been admitted to the ICU for management of metabolic acidosis, hypercapnic respiratory failure and recently diagnosed hospital acquired pneumonia. Dermatology was consulted for evaluation of new onset, asymptomatic, nodular lesions on the face, ears, trunk and arms.

Past Medical History:

CKD IV, AA amyloidosis, COPD, Substance Abuse, Hypertension

Medications:

Albuterol inhaler, Buprenorphine, Hydroxyzine, Naloxone, Trazodone

Allergies:

No known allergies

Family History:

Alcohol abuse

Social History:

Smokes 2 packs of cigarettes per day
Frequently uses opioids and benzodiazepines
Housing instability

Review of Systems:

Endorsed recent bout of diarrhea, shortness of breath, and cough

Physical Examination:

Examination revealed an erythematous papule with overlying crust on the dorsal nose, isolated indurated red nodules on the left cheek and left earlobe, as well as scattered indurated and crusted red to purple nodules on the bilateral lower and upper extremities.

Histopathology:

Skin, left arm, H&E: GMS and PAS stains highlight numerous fungal spores. AFB and Fite stains are negative for mycobacterial organisms. Findings consistent with blastomycosis.

Diagnosis:

Disseminated Blastomycosis

Treatment and Course:

Histopathology findings along with tissue culture that confirmed the growth of blastomycosis prompted an infectious disease consult. This patient had previously been receiving Vancomycin and Zosyn for treatment of presumed hospital acquired pneumonia based on prior CT imaging, however, given the newly detected cutaneous blastomycosis, infectious disease considered that her pulmonary findings were also due to disseminated blastomycosis. Urinary blastomycosis antigen labs were

positive, helping to confirm diagnosis. Amphotericin B was initiated with close monitoring of electrolytes and renal function. This course was originally meant to be for seven days, however, given the patient's hemodynamic stability and impending discharge, this course was shortened to three days in total. She was given a three-day loading dose of itraconazole before being transitioned to 200 mg q12 hours, with the intention of treating her for one year total with close outpatient follow up with infectious disease.

Patient 2:

History of Present Illness:

A 55-year-old female presented to the dermatology clinic for evaluation of skin lesions that had arisen around 6 months prior to presentation. She has recently been treated with Levaquin for pneumonia when she started developing painful skin lesions on the arms, legs, and trunk. At the time of her initial visit with dermatology, only two active nodules on her left 2nd and 3rd fingers remained, but hyperpigmented patches were noted at prior sites of involvement. She denied any recent travel, history of immunosuppression or other systemic signs of infection, including any lingering symptoms of pneumonia.

Past Medical History:

Asthma, OSA, Depression, Hypertension, GERD

Medications:

Azelastine nasal spray, Carvedilol 25 mg BID, Fluoxetine 40 mg daily, Flonase nasal spray daily, Losartan 100 mg daily, Mometasone-formoterol inhaler BID, Nifedipine 60 mg daily

Allergies:

No known allergies

Social History:

Works in a group home
Drinks alcohol socially

Review of Systems:

Negative

Physical Examination:

Dermatologic exam was significant for round hyperpigmented macules with some fine scale at the site of older lesions on her abdomen, right hand, and bilateral lower leg. Two erythematous nodules with central erosions were noted on her left 2nd and 3rd digits. The lesion on the 2nd digit was larger and also contained an overlying pustule.

Histopathology:

Skin, left 2nd digit, H&E: GMS stain highlights yeast with broad-based budding. HSV and CMV immunohistochemical stains are negative. Findings are consistent with cutaneous blastomycosis.

Fungal Culture:

Positive for Blastomycosis

Diagnosis:
Blastomycosis

Treatment and Course:
Based on clinical and histopathology findings, the patient was given a loading dose of itraconazole (200 mg TID for three days) and then continued on 200 mg BID maintenance dosing. She established care with infectious disease who continued the same regimen. She followed up with us two months later and demonstrated resolution of her skin lesions.

Discussion:
Blastomyces is a fungus of Ajellomycetaceae family, with the subspecies *B. dermatitidis* being responsible for the majority of cases of blastomycosis. It is a dimorphic fungus, meaning that at colder temperatures in nature it takes the form of a mold but will transition to a yeast form at 37 degrees Celsius. This fungus is primarily found in hot, damp soil in North America, specifically in the southeast US, Great Lakes as well as Ohio and Mississippi River valleys. A total of 26 states have reported cases of blastomycosis.[1] Exposure to soil represents a risk factor and there is a slightly higher rate of infection in men as compared to women.[2]

The infection typically begins via inhalation of the organism. While in its mold form, Blastomyces is more readily phagocytosed by neutrophils, however, upon heating it will be transformed into its yeast form which is generally too large to be ingested by circulating neutrophils.[3] Many patients, up to 50%, do not go on to have any symptoms at all. Of those with symptoms, these typically develop 3-6 weeks after initial exposure, with the lungs being the most involved organ system, followed by skin, then bone, genitourinary and central nervous systems.[4] Cutaneous disease is typically a result of hematogenous dissemination from the lungs and can often be the presenting or only symptom. While exceedingly rare, primary cutaneous blastomycosis may occur as a result of direct penetration of the skin by the fungus.[5]

In both cases above, the patient had pulmonary symptoms that preceded cutaneous disease, originally diagnosed as bacterial pneumonia. In many cases of blastomycoses, a misdiagnosis of bacterial pneumonia is common and they will often receive multiple rounds of antibiotics before the correct diagnosis is made.[4] Clinically, cutaneous blastomycosis presents with papules, pustules, and verrucous plaques or nodules which may be solitary or multiple. Older lesions may ulcerate and heal with subsequent central cribriform scar formation. More extensive lesions may mimic pyoderma gangrenosum or squamous cell carcinoma.

When blastomycosis is suspected, it is recommended to collect urine antigens, respiratory secretions, as well as skin biopsy and culture.[6] Serologies are not considered to be useful due to relatively low sensitivity and specificity. For patients with pulmonary symptoms, imaging may assist with the diagnosis. The diagnosis is confirmed with visualization of the broad-based budding fungi on microscopy or positive fungal cultures, though this may take 4 weeks to complete. If patients have purulent cutaneous lesions, it is recommended to perform KOH preparations to identify broad based budding yeasts. Histology of lesions that are biopsied may show the yeasts, which can be more readily appreciated using methenamine silver and PAS staining. The surrounding tissue may show pyogranulomatous, pseudoepitheliomatous hyperplasia.

All patients with confirmed blastomycosis, regardless of severity, should be treated with antifungal agents. However, the severity of symptoms, extent of dissemination and immune status of the patient should alter the recommended treatment regimen. Typically, options for treatment include

amphotericin B for severe disease or disease in immunocompromised patients followed by an azole antifungal, usually itraconazole.[7] For severe disease, IV lipid formulation of amphotericin B is recommended daily until clinical improvement is noted, usually 1-2 weeks in duration. Infusion reactions, kidney injury, and electrolyte disturbances are frequent complications of treatment with this agent. After the patient is stabilized, it is recommended to provide a loading dose of itraconazole, 200 mg three times a day for three days, and then a long course of 200 mg twice daily for six to twelve months duration. Patients with mild to moderate disease may be treated with itraconazole without a prior course of amphotericin B. Itraconazole is generally well-tolerated, though it requires gastric acid for absorption and can have significant medication interactions. Additionally, it is not recommended for use in patients with congestive heart failure. Serum levels of itraconazole may be checked two weeks into the treatment course and dosage may be adjusted based on those results. It is recommended to extend treatment with itraconazole to at least 6 months past resolution of skin lesions to minimize chances of recurrence.

Essential Lessons:

- Blastomycosis is a fungal infection seen predominantly in eastern and central United States, where cutaneous findings are often preceded by respiratory disease.
- Severe cases of disseminated blastomycosis should be treated with amphotericin B followed by a prolonged 6-12 month course of itraconazole. Less severe cases may be treated with itraconazole alone.

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Case 5 presented by Allison Ellis, MD PhD, Ola Bode Omoleye, MD, and Roger Haber, MD

History of Present Illness:
A 60-year-old female with a past medical history of diffuse large B-Cell lymphoma (DLBCL) and well-controlled HIV was admitted to the hospital for sepsis. Following a brief ICU admission, the patient was stabilized on intravenous antibiotics and later transferred to the general medicine floor for continued observation.

On day 5 of admission, the patient developed painful, pruritic papules localized to the mons pubis and labia majora. The patient denied a history of a similar rash and did not have similar lesions on the rest of the body. She denied being sexually active for the past year. Recent herpes simplex virus (HSV) testing was negative five months prior.

On day 8 of admission, the papules became hemorrhagic and developed significant associated edema and induration. Dermatology was consulted due to the rapid clinical progression of the skin findings.

Past Medical History:
Diffuse large B-Cell lymphoma (DLBCL) (2008) s/p CHOP (cyclophosphamide/ doxorubicin hydrochloride/ vincristine sulfate/ and prednisone) therapy with remission for >10 years

Relapsing and remitting DLBCL (2023) with metastasis to vaginal canal and significant mediastinal lymphadenopathy complicated by ureteral obstruction s/p 6 cycles of dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) followed by 3 cycles of POLARGO (polatuzumab-vedotin, rituximab, gemcitabine-oxaliplatin), and most recently 1 cycle of R-DHAX (rituximab, dexamethasone, cytarabine, and oxaliplatin)

HIV, Hyperlipidemia, Pre-diabetes

Medications:
Bictegravir/emtricitabine/tenofovir alafenamide, atorvastatin

Allergies:
No known drug allergies

Social History:
Married
Denied tobacco, alcohol, or illicit drug use

Review of Systems:
Pain and swelling of the mons pubis and labia majora

Physical Examination:
Clusters of hemorrhagic vesicles and eroded papules with significant swelling of the bilateral labia majora and mons pubis. No similar lesions were found elsewhere

Laboratory Data/Diagnostic Procedures and Tests:
HSV, VZV, Blastomycosis, Histoplasmosis, Gonorrhea, Chlamydia: negative, HIV PCR: undetectable

Histopathology:
Skin, Mons Pubis, H&E: Histopathological examination revealed a dense and diffuse subepidermal infiltrate of atypical lymphoid cells with large, irregular nuclear contours, hyperchromatic nuclei and indistinct nucleoli. There were numerous mitotic bodies and apoptotic debris in a hemorrhagic background. The epidermis showed acanthosis with mild spongiosis. The neoplastic lymphoid cells were diffusely positive for CD20, BCL2 and BCL6 while negative for CD10.

Diagnosis:
Cutaneous metastasis of DLBCL

Treatment and Course:
Repeat CT chest/abdomen/pelvis revealed significant disease progression including extensive mediastinal lymphadenopathy, extensive retroperitoneal/pelvic lymphadenopathy, and large infiltrative soft tissue mass involving the vagina, uterus and bladder. Skin metastases rapidly progressed into larger, indurated nodules coalescing into plaques.

Due to the rapid disease progression, the patient was started on dexamethasone 40 mg for 4 days followed by Obinutuzumab/Glofitamab Q21D. Chemotherapy regimen was complicated by multiple episodes of hypotension, fever, and tachycardia concerning for cytokine release syndrome. The patient ultimately succumbed to her multiple malignancy related complications following cardiac arrest.

Discussion:
Cutaneous manifestations of DLBCL can be primary or secondary in nature. While primary and secondary cutaneous lymphomas can be similar histologically, they have distinct clinical progression and prognoses.[1,2]

DLBCL is the most common type of non-Hodgkin lymphoma (NHL) and accounts for 25-30% of all NHLs.[3] DLBCL is divided into two subcategories, nodal and extranodal.[3] The clinical presentation typically includes enlarged lymph nodes or a solitary rapidly growing mass with associated B symptoms. [3] The most common sites for extra-nodal involvement are the stomach or gastrointestinal tract followed by the skin.[3,4,5]

Cutaneous metastasis of DLBCL is more commonly seen with nodal disease and has a variable presentation.[1] Multiple nodules or indurated plaques are typically associated with a recent primary diagnosis (<6 months) in comparison to a more distant primary diagnosis (>6 months).[1] Additionally, cutaneous dissemination of DLBCL confers advanced disease as >50% of patients have additional sites of metastasis other than the skin when cutaneous involvement was identified.[1]

Although classified as common site of extranodal disease, [3,4,5] primary cutaneous B cell lymphomas are considered relatively rare, including the subtype primary cutaneous diffuse large B cell lymphoma- leg type (PCDLBCL-LT).[6] PCDLBCL-LT classically presents in an elderly female as a red to brown papule on the distal lower extremity.[6] PCDLBCL-LT is considered an aggressive cutaneous B cell lymphoma subtype based on a 5-year survival rate that is less than 60%.[6] With that said, survival for PCDLBCL-LT is still higher than secondary cutaneous dissemination of DLBCL, which is around 31%.[1]

Lastly, many studies have documented the increased risk of developing lymphoma in patients with HIV, including DLBCL.[7] The correlation between HIV and lymphomagenesis is likely multifactorial, involving immunosuppression, viral co-infection, B-cell dysregulation, elevation of interleukin-10, and elevation of serum free light chains.[7] In cases of HIV associated DLBCL, translocations of MYC and BLC6 are more common and confer high proliferation indices.[7] This patient's previous FISH analysis was negative for translocations, but the patient's recent skin biopsy was BCL6 positive on histology (previously BCL6 negative). Therefore, it is hard to discern if her HIV status, with undetectable viral load, contributed to the rapid, severe progression of her disease.

Taken together, to our knowledge, no previous case has reported rapid and localized involvement of the skin in a case of long-standing DLBCL. Therefore, this case highlights a unique presentation of eruptive, secondary cutaneous DLBCL in a patient with HIV. Given the poor prognosis associated with systemic DLBCL with cutaneous dissemination, timely skin biopsies followed by multidisciplinary care is of utmost importance. Early, aggressive treatment of DLBCL with secondary skin metastasis can improve survival, highlighting the importance of a prompt diagnosis, especially in those with atypical presentations.[8]

Essential Lessons:

- Cutaneous dissemination of DLBCL is a relatively rare phenomenon that has a poor prognosis in comparison to primary cutaneous B cell lymphomas.
- The clinical presentation of cutaneous dissemination of DLBCL is variable. If present, numerous nodules or indurated plaques are typically seen within 6 months of the primary diagnosis of DLBCL.
- HIV associated DLBCL is associated with MYC and BCL6 translocations and typically confers a more rapidly progressive disease course.

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Case 6 presented by Joshua Burshtein, MD, Ola Bode Omoleye, MD, Pedram Gerami, MD, Roger Haber, MD, Maria Tsoukas, MD, PhD

History of Present Illness:
A 35-year-old female presented for evaluation of an asymptomatic lesion on her thigh that had been rapidly growing in size since first appearing two years ago. She denied similar lesions in the past as well as a personal and family history of skin cancer.

Past Medical History:
None

Past Surgical History:
None

Medications:
None

Allergies:
No known drug allergies

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

Review of Systems:
Negative for itching, burning, or pain.

Physical Examination:
Skin exam was significant for a 1.1 x 1.0 cm hyperkeratotic dark blue papule on the left anterior thigh.

Histopathology:
Skin, left thigh, H&E: LAMTOR1-PRKCA Fusion Epithelioid Blue Tumor of Uncertain Malignant Potential

Dermal, heavily pigmented melanocytic proliferation comprised of spindled to dendritic melanocytes with numerous densely pigmented melanophages. Occasional scattered mitotic figures and neutrophils are present. The adjacent dermis shows squamous pearls with dyskeratotic keratinocytes. The overlying skin is ulcerated with adjacent hyperkeratotic and invaginated epidermis showing papillomatosis, parakeratosis, hypergranulosis, and melanin pigmentation.
SOX10 and HMB45 were diffusely positive.
Melanocytes are positive for MART1 and Ki-67 at a proliferation rate of 5%.

Consultation at Northwestern University Dermatopathology Department for further expert opinion with the following addendum (generated by expert dermatopathologist Dr. Pedram Gerami).

Addendum:
Compound melanocytic neoplasm with epidermal ulceration and sheet-like growth pattern of intermediate-sized melanocytes with moderate nuclear atypic and mitotic activity of 3/mm^2.

FusionPlex solid tumor assay and the NM expanded panel were performed, and the only definitive pathogenic variant identified was LAMTOR1-PRKCA fusion.

Diagnosis:
LAMTOR1-PRKCA Fusion Epithelioid Blue Tumor

Treatment and Course:
After receiving the histopathological report, the patient was scheduled for excision. The tumor was excised with 1cm margins, and the defect was repaired with a layered closure. Final histopathology showed residual epithelioid blue tumor with negative margins of resection.

Discussion:
Epithelioid blue nevus (EBN) is a type of melanocytic tumor that appears clinically as a blue-black pigmented papule or nodule. EBNs most often develop in patients with Carney complex, a syndrome characterized by various cutaneous and mucosal lesions in addition to both endocrine and nonendocrine tumors. Genetically, the two most common alterations in EBNs are fusion of protein kinase C alpha (PRKCA) and inactivating mutations in protein kinase cAMP-dependent type I regulatory subunit alpha (*PRKAR1A*)[1,2]. PRKCA is typically involved in diverse cell functions including proliferation, differentiation, survival, and migration, and fusions of this protein can result in overactivation of its kinase domain[1,2].

EBNs with PRKC fusions typically occur in younger patients (median age 16 years) though there is a wide age range of reported cases for the different fusion types (3 months to 71 years of age)[3–5]. Notably, the patient in this case is significantly older than prior reported patients with EBNs with LAMTOR1-PRKCA fusions (6 to 16 years of age)[3]. Most reported EBNs with PRKC fusions occur on the head and neck. However, development is not directly associated with sun exposure and can include sites such as the buttocks, proximal legs, and feet[1,3].

Clinical differential diagnoses include melanoma, blue nevus, nonmelanoma skin cancer, keratoacanthoma, congenital melanocytic nevus, and dysplastic nevus. Diagnosis relies on histological and immunohistochemical analysis[5,6]. PRKCA fusion EBNs are composed of epithelioid melanocytes with variable pigmentation forming solid aggregates[3]. At the edges of the lesion, there may be aggregates of spindle-shaped melanocytes[3]. Most reported fusion EBNs have moderate nuclear atypia, absent ulceration, and mitotic index $\leq 2/mm^2$[2,3]. Those with larger, more atypical epithelioid melanocytes are often diagnosed as epithelioid blue tumors (EBTs). Diagnosis is challenging as there is histologic overlap with other melanocytic lesions such as cellular blue nevus and malignant blue nevus. The patient's EBN had histological and immunohistochemical findings consistent with fusion EBT and demonstrated a greater mitotic activity ($>3/mm^2$) than previously reported cases.

As the literature on PRKCA fusion EBNs primarily comprises case reports with limited prognostic data, treatment typically consists of excision and clinical monitoring. There is a favorable prognosis of fusion EBNs. A meta-analysis of cases with PRKC fusions found that in 34 patients with an average follow-up time of 18.3 months, local recurrence occurred in two (5.9%) patients, one at three months after excision and the other at 13 months[3]. There was no further recurrence after more than one year of follow-up in these patients[3]. No cases had documented distant metastasis[3]. One patient with EBT had a positive sentinel lymph node biopsy and subsequently underwent complete right posterior cervical chain lymph node dissection. This case had no positive cervical lymph nodes and no evidence of recurrence after nine years of follow-up[3]. Further, for the three prior cases of

LAMTOR1-PRKCA fusion EBN, follow-up data was available for two cases. After five- and fifty seven-month follow-ups respectively, neither patient had evidence of recurrence. However, there are rare reports of progression of PRKCA fusion EBNs to melanoma via BAP1 inactivation[5]. While there is no consensus on follow-up protocol due to the paucity of literature on prognosis and follow-up of fusion EBTs, evidence suggests close clinical monitoring for local recurrence is necessary for several years.

LAMTOR1-PRKCA fusion EBT is a unique tumor that can be a source of patient concern. This case highlights the importance of thorough investigation to arrive at a diagnosis such that appropriate intervention can be implemented. As there is limited literature on this type of fusion EBN, this case provides valuable insight into diagnosis and management for clinicians.

Essential Lessons

- Epithelioid blue nevus is a rare growth that occurs due to fusion of *PRKCA* or inactivating mutation in *PRKAR1A.* It is important to distinguish from melanoma and nonmelanoma skin cancer and diagnosis relies on histological analysis.
- Literature on follow-up is limited, though most patients have an excellent prognosis. Close clinical monitoring is suggested to evaluate for local recurrence.

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Case 7 presented by Alexander Woods MD, Wenhua Liu MD, Roger Haber MD

History of Present Illness:
A 33-year-old female presented for hair loss on the scalp for 1 year, which had worsened over the past 3 months with the development of several plaques on the vertex of her scalp. She reported tenderness and occasional pruritus. She had not tried any topical or oral medications for this condition. There were no recent changes to any of her medications. Of note, the patient was 3 months pregnant at the time of presentation. She reported no issues with the current or any previous pregnancies. She denied joint pain, oral or genital lesions, fatigue, excessive sun exposure, or any symptom associated with sun exposure. She denied a family history of lupus.

At multiple follow-up visits throughout four years, she continued to develop new plaques, including multiple on her cheeks and behind her ears at the contact points of her glasses.

Past Medical History:
G6PD deficiency, asthma, benign essential hypertension, hyperlipidemia, peripartum cardiomyopathy, pulmonary embolism, morbid obesity

Past Surgical History:
Cholecystectomy

Family history:
Mother with Mixed Connective Tissue Disease

Medications:
Carvedilol 25 mg BID, lisinopril 30 mg QD, hydralazine 50 mg BID, albuterol 90 mcg/actuation inhaler, escitalopram 20 mg QD, phentermine-topiramate 11.25-69 mg QD, atorvastatin 20 mg QD, buspirone 10 mg QD

Allergies:
No know drug allergies

Social History:
Denied smoking, alcohol, or illicit drugs

Review of Systems:
The patient denied any joint pains, oral or genital erosions, or fatigue

Physical Examination:
On initial presentation, vertex scalp with three small oval atrophic plaques with adherent white scale and peripheral hyperpigmented border, one large atrophic erythematous plaque with central yellow adherent scale and crusting with peripheral hyperpigmented border within a large area of scarring alopecia on the vertex scalp.

On follow-up, the scalp revealed alopecic violaceous hyperkeratotic plaques with ulceration and scarring. Round pink to purple plaques with a rim of hyperpigmentation were observed on her bilateral cheeks, nose, retroauricular areas at the contact points of her glasses, and bilateral upper arms.

Histopathology:
Initial punch biopsy of the scalp in March 2022 revealed absent epidermis and melanophages in the papillary dermis with perivascular, perineural, and perimuscular lymphocytes and stromal mucin. DIF positive for IgG, IgM, IgA, C3, and fibrinogen deposition in the DEJ and basement membrane of adnexal structures.

A biopsy of the right arm in December 2022 revealed a vacuolar interface change with dyskeratotic keratinocytes and foci of parakeratosis. Infiltrate of lymphocytes, histiocytes, and rare eosinophils. Perivascular lymphocytic infiltrate with increased derm mucin, consistent with lupus erythematosus.

Diagnosis:
Discoid Lupus Erythematosus with Koebner Phenomenon

Treatment and Course:
Her laboratory results in October 2020 were negative for antinuclear antibody (ANA), anti-SSA, n, and anti-SSB antibodies. Positives included hemoglobin 10.1 and MCV 73.2.

In November 2022, labs revealed positive anti-ribonucleoprotein acid (anti-Smith/RNP) antibodies 58 (nl < 19) and speckled ANA cytoplasmic pattern at a titer of 1:160, but negative anti-smith, anti-dsDNA, anti-SSA, anti-SSB, anti-Scl-70, anti-Jo 1 antibodies.

In August 2024, labs revealed anti-dsDNA IgG ELISA 120 (nl < 24), anti-dsDNA IFA titer 1:80, anti-smith/RNP 70 (nl < 19), and anti-smith 59 (nl < 40) antibodies. ESR 77 (nl < 20). Complement C3 and C4, and CRP were unremarkable. UA revealed 100 mg/dl protein, 1+ blood, and a protein/creatinine ratio of 0.76. CBC again revealed microcytic anemia.

She was originally managed with hydroxychloroquine 200 mg BID and topical corticosteroids—clobetasol 0.05% ointment BID to lesions on her scalp and arms, fluocinonide 0.05% ointment BID to lesions on her face. However, she was uncontrolled with this alone, and on the most recent follow-up, methotrexate 10 mg weekly was added with folic acid. Intralesional corticosteroid injections were also intermittently utilized for the treatment of scalp lesions. Her recent blood work with systemic lupus erythematosus (SLE)-specific antibodies, as well as her history of DLE, meets the criteria for progression to SLE.

Discussion:
The Koebner phenomenon, or the isomorphic response, refers to the appearance of disease-specific lesions on previously unaffected skin following trauma.[1] It is well-documented in dermatologic conditions, including psoriasis, vitiligo, lichen planus, and dermatomyositis, but less commonly in discoid lupus erythematosus (DLE).[1-5] Herein, we describe a patient with Koebnerizing DLE, where trauma from eyeglasses induced discoid lesions on the cheeks and nose.

Triggers of Koebnerization include environmental stresses such as scratches, sun exposure, scars, and tattoos.[5] The pathogenesis is theorized to have an initial non-specific inflammatory step that releases cytokines, stress proteins, adhesion molecules, or autoantigens, followed by a disease-specific immune response involving T-cells, B-cells, autoantibodies, and immune deposits, which are influenced by genetic predisposition.[5]

Koebnerization has been reported in DLE and dermatomyositis.[2,5] In both, trauma-induced activation of keratinocytes and immune cells release cytokines and chemokines, which promote inflammation

and lesion formation.[5] Elevated interferon pathways contribute to the pathogenesis of dermatomyositis and DLE. In DLE, interferon pathways play a significant role through plasmacytoid dendritic cells and keratinocytes, which establish a self-amplifying inflammatory loop driven by type I interferons.[2] The presence of Koebnerization in both dermatomyositis and DLE suggests that trauma-induced activation of interferon pathways might be a common pathogenic mechanism in these conditions, contributing to the chronic inflammatory lesions observed in both diseases.

While there are reports of the Koebner phenomenon following a tattoo, there are no documented cases associated with repeated microtrauma from eyewear in patients with DLE.[5] Our patient developed symmetric discoid lesions at the points of contact with her eyeglasses on her cheeks and nose. The chronic friction and pressure from the eyeglass frames likely induced these DLE lesions. While in other conditions, such as vitiligo, Koebnerization is associated with active disease, it is not well elucidated if this indicates a similar disease state in DLE.[1] Further research is necessary to determine if Koebnerization is a reliable marker of active DLE and whether it has prognostic implications portending a higher risk for systemic lupus erythematosus, as were both the case for our patient.

Recognition of Koebnerization in DLE is important as it may indicate active or poorly controlled disease. Patients with conditions that can exhibit the Koebner phenomenon, such as DLE, should be counseled on preventing avoidable trauma, including extra caution with essential items like eyeglasses. Furthermore, patient's exhibiting Koebnerization in DLE should be monitored closely for signs of development of SLE, including repeat diagnostic testing when appropriate. Further research is needed to understand the implications of developing the Koebner phenomenon in DLE and its potential role in indicating disease activity, as well as to guide management strategies.

Essential Lesson:

- Koebnerization in patients with DLE is a rare phenomenon that may signal uncontrolled DLE and portend eventual development of SLE, as in our patient
- Physicians should consider extensive, and even repeat screening, such as in our patient, in patient's exhibiting DLE with Koebnerization
- Awareness of this association from a physician and patient perspective can aid in the management of DLE and detect early progression to SLE

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Case 8 presented by Lacey Zimmerman, MD, Saul Turcios Escobar, MD, Michelle Bain, MD, and Olaoluwa Bode-Omoleye, MD

History of Present Illness:
A 2-month-old female presented for evaluation of a dark lesion on her scalp that had been present since birth. Her parents were unsure if the lesion was changing over time. She was otherwise healthy. There were no reported issues during pregnancy, and she was born full-term via vacuum-assisted delivery. There was no family history of atypical nevi or melanoma. Both paternal grandparents had kidney cancer.

Past Medical History
None

Medications:
None

Allergies:
No known drug allergies

Social History:
Lives at home with parents and a 2-year-old sibling.

Review of Systems:
Feeding and sleeping well. Normal growth and development.

Physical Examination:
4x3 mm papule on the right temporal scalp with dark brown/black amorphous, homogenous pigment anteriorly and lighter brown globular pigment pattern posteriorly with irregular borders. No preauricular, postauricular or cervical lymphadenopathy was palpated.

Histopathology:
Microscopic examination of a 5 mm punch biopsy revealed a combined pattern melanocytic neoplasm composed of conventional nevomelanocytes intermixed with large expansile aggregates of epithelioid melanocytes with more pigmented cytoplasm. These nests of atypical, pigmented melanocytes were arranged in a plexiform pattern aggregating along adnexa and the neurovascular bundle. The nuclear atypia varied from moderate to severe, and the mitotic count was 4 per mm^2 focally. Immunohistochemical stains showed the melanocytic proliferation was diffusely positive for HMB45 and SOX10. MART-1/Ki-67 (multiplex stain) showed the melanocytes were positive for MART-1 with a Ki-67 proliferation rate of approximately 5%. Expression of p16 was lost. Molecular analysis revealed the presence of CTNNB1 p.(T41I) and BRAF V600E pathogenic variants consistent with a diagnosis of a deep penetrating nevus.

Due to the rarity and complexity of the case, expert consultation was sought. The above histopathological results were determined with the assistance of Pedram Gerami, MD, of Northwestern Medicine.

Diagnosis:
Severely atypical deep penetrating nevus

Treatment and Course:
The patient underwent complete excision under general anesthesia at Lurie Children's Hospital. The procedure was uncomplicated, and she is doing well with no evidence of recurrence nor lymphadenopathy at 4 months following the surgery. She will continue to undergo close clinical monitoring.

Discussion:
Deep penetrating nevi (DPN) are rare melanocytic lesions that can display atypical histological characteristics, making it challenging to distinguish them from malignant melanoma. While conventional DPN are generally regarded as benign, atypical or borderline DPN have been reported to spread to lymph nodes and progress to melanoma.[1-2]

On physical exam, typical DPN usually appear as a single papule or nodule that is well-defined, symmetrical, nonulcerated, dome-shaped, and darkly pigmented, sometimes with more than one color present. Dermoscopy findings have not been well established.[2] As clinical findings for these lesions are nonspecific and the differential diagnosis is broad, including Spitz nevus, pigmented spindle cell nevus, blue nevus, and malignant melanoma, pathologic examination is crucial.[3]

On histology, typical DPN are typically well-demarcated, symmetrical lesions characterized by spindled or epithelioid melanocytes. These cells are arranged in fascicles, cords, and nests that extend into the deeper layers of the dermis and subcutaneous tissue, forming an inverted triangle or wedge shape.[1-2] A plexiform pattern is commonly seen, and the bundles of melanocytes are frequently associated with adnexal and neurovascular structures. Mitotic figures are rarely present in typical DPN. DPN can occur in isolation but are frequently seen as part of a combined nevus along with a conventional, blue or Spitz nevus.[2]

When DPN exhibit atypical features, such as asymmetry, poor circumscription, and/or increased mitotic activity, the differentiation from melanoma becomes more complex. According to the World Health Organization Classification of Skin Tumors, the criteria for atypical DPN includes diameter >5 mm, asymmetry, poor circumscription, moderate to severe cytologic atypia, and mitotic activity greater than 2 per mm^2.[4] As further atypia is identified, the concern for melanoma increases. DPN-like melanoma shares histological characteristics with conventional DPN but exhibits additional atypical features. These include pagetoid spread with abnormal melanocyte migration upwards through the epidermis, irregular thickening or thinning of the epidermis, invasive or nodular growth at the base of the lesion, increased tumor depth, ulceration, necrosis, and/or inflammatory responses. Perineural and lymphovascular invasion may also be present, along with marked cytologic abnormalities and mitotic activity, including atypical mitotic figures.[2] In contrast to typical and atypical DPN, the atypia in DPN-like melanoma is nonrandom and present throughout the lesion.[2-3]

Immunohistochemical and molecular studies are often utilized to help distinguish DPN from melanoma. DPN are typically diffusely positive for HMB45, SOX10, S100, and MART-1.[2] PRAME is usually negative in DPN[2] but positive in melanoma.[5] Ki-67 proliferative index is low (less than 5%) in typical DPNs, and while it may be increased in atypical DPN, it is higher in melanoma (usually 10% or greater). Complete loss of p16 expression has been associated with DPN-like melanoma.[2,5] In molecular analysis of DPN, mutations of CTNNB1 are common, and mutations of BRAF (particularly V600E) can be seen. Additional genetic mutations, such as alterations in CDKN2A, TERT and other genes, are seen in DPN-like melanoma.[2]

DPN are not associated with a family history of melanoma.[3] Most DPN occur in females, appear on the head or neck, are acquired, and present before the age of 30.[1] Congenital DPN have rarely been reported.[1,3] We believe our patient, with a severely atypical DPN reported to be present at birth and diagnosed at two months of age, is exceptionally rare. To the best of our knowledge, she is the youngest patient ever documented with a confirmed diagnosis of a DPN. In a recent systematic review of 403 typical and atypical DPN cases, only one infant was reported—a 3-month-old male with a typical DPN that developed within a congenital nevus.[1,6] The youngest patient with an atypical DPN in the review was 4 years old. While most DPN have benign behavior, this review of 355 typical DPN and 48 atypical DPN cases, with follow-up periods ranging from 4 months to 23 years, reported 6 cases with local recurrences (2 typical DPN and 4 atypical DPN patients) and 12 cases with positive sentinel lymph node biopsy (SLNB) (all atypical DPN patients), 3 of which died with widespread metastatic disease.[1]

A range of treatment strategies have been employed for cases of atypical DPN, including no further intervention after the initial biopsy, re-excision with varying margins (conservative to wide), SLNB, radical lymphadenectomy, and systemic therapy. The most cautious approach would be to treat these cases as melanoma. Factors such as patient age and the degree of atypia influence management decisions. SLNB biopsy remains controversial and is not considered standard management. Although deposits in sentinel lymph nodes may be common in atypical DPN, evolution into melanoma and fatalities are rarely reported. In cases with significant atypia or uncertainty regarding the diagnosis, a more aggressive surgical approach, including SLNB and wider excision, may be justified. Some experts suggest that atypical DPN should be completely excised with wide margins of up to 1 cm. Although there are no definitive clinical guidelines, long term, periodic clinical monitoring, including full-body examinations, is also recommended.[2]

Essential Lessons:

- DPN can be challenging to distinguish from melanoma, especially atypical variants, which have also been reported to progress to melanoma.
- Understanding the nuances of DPN is crucial for accurate diagnosis and appropriate management.

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