Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, November 9, 2016
Gleacher Center – Chicago, IL

Conference Host:
Department of Dermatology
Feinberg School of Medicine
Northwestern University
Chicago, Illinois

Program

Host: Northwestern University

Conference Location

Gleacher Conference Center
450 N. Cityfront Plaza Dr., Chicago

All meeting activities take place on the 6th Floor of the Gleacher Center.

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *6th Floor Lobby and Room 600*
8:30 a.m. - 10:00 a.m.	**Clinical Rounds** Patient Viewing – *Rooms 602 and 604* Posters – *North Foyer (available throughout the morning)* Slide viewing – *Room 608 (available throughout the morning)*
9:00 a.m. - 10:00 a.m.	**Resident/Basic Science Lecture** – *Room 621* "Allergens Review" *David E. Cohen, MD, MPH*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors** – *Room 600*
10:30 a.m. - 12:00 p.m.	**Resident Case Presentations & Discussion** *Room 621*
12:00 p.m. - 12:15 p.m.	**MOC Self-Assessment Questions** *Room 621*
12:15 p.m. - 12:45 p.m.	**Box Lunches & visit with exhibitors** *Room 600*
12:45 p.m. - 1:00 p.m.	**CDS Business Meeting** *Room 621*
1:00 p.m. - 2:00 p.m.	**General Session** – *Room 621* *BLUEFARB LECTURE*: "Trends in Contact Dermatitis" *David E. Cohen, MD, MPH*
2:00 p.m.	**Meeting adjourns**

Mark the Date!
Next CDS monthly meeting – Wednesday, December 7, 2016 at the Gleacher Center
Hosted by the University of Chicago; Guest speaker: Victor G. Prieto, MD, PhD
Department Chair, Department of Pathology, Division of Pathology/Lab Medicine, The University of Texas MD Anderson Cancer Center; Houston, TX

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

CME Information

This educational activity is jointly provided by AXIS Medical Education, Refine Me CE and the Chicago Dermatological Society

Overview

The Chicago Dermatological Society was established in 1903 and has strived to provide meaningful educational opportunities to dermatologists in the Chicago area for more than a century. Guest speakers from across the country share their expertise with CDS members, as well as residents in training medical students doing their dermatology rotation. CDS schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. In addition to two lectures given by the guest speaker, the residents of the host institution present cases which are offered for audience discussion. In addition, live patients, posters and microscopic slides prepared by the residents are made available during the "clinical rounds" portion of the meeting. CDS also offers a 15-minute session that qualifies for "Maintenance of Certification" self-assessment questions under the auspices of the American Board of Dermatology.

Target Audience

This activity has been designed to meet the educational needs of dermatologists. CDS members, residents in training and medical students engaged in their dermatology rotation are invited to attend.

Learning Objectives

At the conclusion of the 2016/17 series of meetings, the participant should be able to:

1. Discuss key factors in the diagnosis and treatment for viral diseases and bacterial infections.
2. Describe the manifestation of skin cancers and the efficacy of treatments available to the dermatologist.
3. List the therapeutic options available to the dermatologist for a variety of skin diseases, both medical and surgical, and discuss how new emerging treatments can be successfully incorporated into a dermatology practice.

Physician Accreditation Statement

This activity is planned and implemented by AXIS Medical Education, Refine Me CE and the Chicago Dermatological Society. AXIS Medical Education is accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC) to provide continuing education for the healthcare team.

Credit Designation for Physicians – AXIS Medical Education designates this live activity for a maximum of 4.75 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendees are required to submit a CME claim form upon departure from the conference. Please leave your form, along with the attached evaluation form, at the registration table when you leave the meeting. Thank you for your attention to this important item.

Disclosure of Conflicts of Interest

AXIS Medical Education requires instructors, planners, managers and other individuals and their spouse/life partner who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by AXIS for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All speakers are expected to follow the "first slide" rule to repeat their conflict of interest disclosures during their talk.

Today's guest speaker, David E. Cohen, MD, MPH, has disclosed the following relationships: Director - Dermira, Topica; Consultant - Medimetriks, Ferndale, Almarill; Ownership interest - Dermira, Topica, Medimetriks. The following have no conflicts to disclose: Residents presenting cases at this meeting; planning committee members - Alix Charles, MD, program chair and CDS president; Julie Moore, MD, CDS past-president; Richard Paul, CDS Executive Director; Ronald Viggiani, MD and Dee Morgillo, MEd, MT(ASCP), CHCP, AXIS Medical Education.

AXIS Contact Information

For information about the physician accreditation of this program please contact AXIS at 954-281-7524 or info@axismeded.org.

Americans with Disabilities Act

In compliance with the Americans with Disabilities Act, we will make every reasonable effort to accommodate your request. For any special requests, please contact the CDS at: Rich@ChicagoDerm.org.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Dislosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

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FEINBERG SCHOOL OF MEDICINE
DEPARTMENT OF DERMATOLOGY

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Namita Jain, MD, MPH (PGY-3)
Lida Zheng, MD (PGY-2)

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CHICAGO DERMATOLOGICAL SOCIETY **Case #1**

Presented by Sreya Talasila, MD and Joaquin Brieva, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 50-year-old previously healthy Caucasian female was referred to dermatology for evaluation of a pruritic, faintly erythematous truncal eruption present for 4 months. Concurrently, she had been following with hepatology for work-up of incidentally noted transaminitis on routine blood work, the etiology of which was suspected to be autoimmune hepatitis and for which she was being treated with a prednisone taper.

On review of systems, she reported previous development of painful vaginal lesions several months prior. She had been diagnosed with candidal vaginitis and treated with an oral antifungal without improvement. She was eventually prescribed valacyclovir, and the lesions resolved.

PAST MEDICAL HISTORY

Degenerative joint disease

SOCIAL HISTORY

Married, reports being in a monogamous relationship with her husband

MEDICATIONS

Multivitamin

PHYSICAL EXAM

Upper extremities and trunk with faintly erythematous, monomorphic, vaguely annular macules and patches. Palms and soles clear. Oral cavity clear.

LABS/IMAGING

Abnormal:

Labs: ALT 101 (ref. 8-40), AST 67 (ref. 8-40), alkaline phosphatase 611 (ref. 33-115), GGT 196 (ref. 3-55), anti-treponemal antibody positive, RPR 1:1024

Ultrasound abdomen: The liver demonstrates heterogeneous echotexture with a focal area of decreased echogenicity within the posterior segment of the right lobe measuring 2.8 cm.

MRCP: Multiple lesions with a "target" appearance are present throughout both lobes of the liver. The diagnostic considerations include metastatic lesions.

CT abdomen: Multiple heterogeneously enhancing hepatic masses representing metastases until proven otherwise. A less likely diagnosis is hepatic vasculitis.

PET/CT: There are multiple hypermetabolic lesions scattered throughout the liver, most numerous in the right lobe. These have very increased metabolic activity consistent with multiple hepatic metastases. There is no definite localization of a primary malignancy.

Normal/Negative: CBC, BMP, total bilirubin, direct bilirubin, total protein, CRP, ESR, ANA, hepatitis A/B/C serologies, HIV Ag/Ab, leptospira IgM, Lyme DNA, *Borrelia burgdorferi* IgM and IgG

HISTOPATHOLOGY

Skin biopsy: Mild interface and perivascular dermatitis. Immunohistochemistry for anti-treponemal antibody is negative.

Liver biopsy: Liver parenchyma with necrotizing scarring nodules, acute inflammation characterized by a lymphoplasmacytic infiltrate and focal necrosis, consistent with inflammatory pseudotumor-gummatous lesions. *Treponema pallidum* immunostaining was positive for spirochetal bacteria, supporting the diagnosis of spirochetal bacteria-associated gumma.

DIAGNOSIS

Tertiary hepatic syphilis overlapping with secondary cutaneous syphilis

TREATMENT AND COURSE

The patient was treated with 14 days of IV penicillin G followed by 7 days of IM penicillin G given concern for neurosyphilis (due to patient's report of vision changes). Her cutaneous findings quickly resolved. There was significant interval resolution of hepatic lesions on follow-up imaging.

DISCUSSION

Syphilis is a sexually transmitted disease caused by the spirochete *Treponema pallidum*. Syphilis progresses through four stages, which represent a continuum, and symptoms of different stages may overlap.

Primary syphilis typically presents as a painless solitary chancre at the site of inoculation 10-90 days after exposure. The chancre resolves spontaneously in one to four months. Without treatment, blood-borne spread of *T. pallidum* results in secondary syphilis, which presents weeks to months after the chancre appears. The skin is most frequently affected with a symmetric erythematous macular and papular rash on the trunk and proximal extremities, including the palms and soles. Condylomata lata are also associated with secondary syphilis, which presents as soft, verrucous plaques on mucosal surfaces. During the latent stage, skin lesions resolve, however serologic tests remain positive. Tertiary or late syphilis develops years after the initial infection and can involve any organ system. Cutaneous tertiary syphilis manifests with gummatous lesions (papules, nodules, and papulonodules that commonly ulcerate). Gummas, which histologically are seen as granulomas, result from a delayed hypersensitivity reaction to the spirochete.

CNS involvement can occur during any stage of syphilis. If clinical evidence of neurologic involvement is present, a CSF examination should be performed. Syphilitic uveitis is common, and an ophthalmologic evaluation should be performed for any ocular complaints. Hepatic involvement is rare in tertiary syphilis. The clinical picture can be mistaken for hepatic metastasis, as in this case.

The clinical conundrum with this patient is the timing of her infection. There are cases reported of late syphilis presenting only 1 year after infection. This patient may have had accelerated tertiary syphilis due to immunosuppression secondary to her treatment with prednisone. This has not been previously reported in the literature. However, syphilis is known to progress rapidly in patients with HIV, so it is conceivable that other means of immunosuppression would result in more rapid progression to tertiary syphilis.

KEY POINTS

1. Syphilis is a "great mimicker" with protean cutaneous manifestations.
2. Syphilis may progress rapidly through its four stages, which overlap, in immunosuppressed patients.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #2**

Presented by Brittany Dulmage, MD and Ahmad Amin, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 29-year-old African American female presented with a 1-month history of pruritic papules that started on her arms and spread to her face and legs, which were pronounced within her tattoos. She also endorsed nausea, hot flashes, fatigue, and mild shortness of breath.

PAST MEDICAL HISTORY

None

MEDICATIONS

None

PHYSICAL EXAM

Bilateral eyebrows and glabella have prominent, deeply indurated skin folds leading to a leonine appearance. Prominent madarosis of the bilateral lateral eyebrows. Innumerable tightly clustered 1-3 mm skin-colored to pink, indurated, firm, monomorphic papules over the arms, legs, and back.

LABS/IMAGING

Abnormal: SPEP and immunofixation showed monoclonal protein IgG lambda
Normal/Negative: CBC with differential, CMP, CPK, UPEP, hepatitis panel, ANA, TSH, HSV serologies, echocardiogram, bone marrow biopsy, bone survey

HISTOPATHOLOGY

The epidermis is unremarkable. Within the reticular dermis, there is a proliferation of haphazardly arranged prominent fibroblasts embedded in a myxoid stroma. Colloidal iron stain demonstrates dermal deposits of acid mucopolysaccharides.

DIAGNOSIS

Scleromyxedema

TREATMENT AND COURSE

The patient was started on bortezomib and methylprednisolone therapy with improvement in her skin and stabilization of immunoglobulin levels. To ensure durable disease control, she plans to undergo autologous hematopoietic stem cell transplantation.

DISCUSSION

Scleromyxedema is a cutaneous mucinosis that is characterized clinically by a generalized papular and sclerodermoid eruption in the setting of a monoclonal gammopathy. Histopathological features of scleromyxedema include mucin deposition, increased spindle-like fibroblast proliferation, and fibrosis. Additionally, diagnosis of scleromyxedema requires the absence of thyroid dysfunction. Middle-aged adults are most commonly affected, and the disease does not have a predilection for either gender.

Patients with scleromyxedema almost universally present with 2-3 mm, tightly spaced papules involving the hands, neck, and head, particularly the glabella and post-auricular areas. Without

treatment, papules will continue to appear and may coalesce. Unlike scleroderma and scleredema, there are no focal areas of sparing in advanced disease. Involved skin in scleromyxedema may be indurated leading to additional typical clinical features of leonine facies, microstomia, and the "donut sign" over affected proximal interphalangeal joints. Affected skin may be, but is not always, intensely pruritic.

Paraproteinemia, typically IgG lambda, is observed in more than 80% of patients with scleromyxedema. When features of scleromyxedema are present but a monoclonal protein is not detected, localized papular mucinosis should be considered. An atypical variant of scleromyxedema lacking a detectable monoclonal protein has also been proposed. A case of scleromyxedema with monoclonal protein detection in lesional skin but not peripheral blood has also been reported.

Dysphagia with reduced proximal esophageal motility or aperistalsis as well as myopathy are commonly reported systemic manifestations of scleromyxedema. Fatal cases of scleromyxedema due to systemic involvement have also been reported including cardiopulmonary failure in the setting of mucin deposition in coronary and pulmonary vessels and myocardium. Fatal central nervous system (CNS) involvement including encephalopathy, seizures, and coma has been reported with unknown etiology and no mucin deposition identified in CNS tissues.

Historically suggested first-line treatments include melphalan, systemic corticosteroids, and plasmapheresis. More recently, reported cases have been treated with thalidomide, lenalidomide, bortezomib, IVIG, and autologous stem cell transplantation. Bortezomib is a proteasome inhibitor which induces cell-cycle arrest and apoptosis of plasma cells. In a case series of 13 patients treated with IVIG, all showed complete or partial response; however, the effect of IVIG is temporary with return of disease in the absence of maintenance therapy.

KEY POINTS

1. Diagnosis of scleromyxedema is made in patients with a papular cutaneous eruption, monoclonal gammopathy, and no thyroid dysfunction who have a skin biopsy showing mucin deposition, increased collagen and spindle-like fibroblasts.
2. Subsets of patients with scleromyxedema will develop systemic symptoms including possibly fatal cardiopulmonary or CNS involvement.
3. Treatment options for scleromyxedema include bortezomib, thalidomide, lenalidomide, IVIG or autologous stem cell transplantation.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #3**

Presented by Amin Esfahani, MD[1], Cristina Isales, MD[2], Lacey Kruse, MD,[3] and Pedram Gerami, MD[1]
[1]Department of Dermatology, Feinberg School of Medicine, Northwestern University
[2]Department of Pathology, Feinberg School of Medicine, Northwestern University
[3]Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A full-term 3-month-old African American girl presented with a growth on the scalp. The lesion was first noted at birth and was initially thought to be a keloid. Her parents noted that the growth had gradually enlarged over the past three months of life. The patient was otherwise healthy.

PAST MEDICAL HISTORY

Born at 39 weeks via Cesarean section for transverse lie

MEDICATIONS

None

FAMILY HISTORY

No family history of skin cancer

PHYSICAL EXAM

13 cm hyperpigmented, hypertrichotic thin plaque on the left temporal, parietal, and occipital scalp. Within this plaque, on the left parietal scalp, there was a 4.8 cm x 2.5 cm firm, hyperpigmented lobulated exophytic nodule.

HISTOPATHOLOGY

Left parietal scalp: malignant melanoma, Breslow depth 2.75 mm, Clark's level IV, without ulceration, mitotic count of 12/mm^2

- Fluorescence *in situ* hybridization (FISH) showed segmental chromosomal aberrations in 6p25 in greater than 80% of enumerated cells
- Genetic testing significant for an activating mutation in pathogenic variant of *NRAS*

Left scalp: intradermal nevus, congenital type

PRELIMINARY DIAGNOSIS

Malignant melanoma arising within a large congenital melanocytic nevus

TREATMENT AND COURSE

The patient underwent a wide local excision (WLE), repaired with a split-thickness skin graft, and sentinel lymph node biopsy. Histopathology of the WLE revealed a Breslow depth of 8mm. A proliferative nodule was also noted in this specimen. Two out of five sentinel lymph nodes were positive for malignant melanoma (largest deposit 1.3 mm x 0.2 mm). PET-CT demonstrated increased metabolic activity in the left posterior cervical lymph node basin concerning for metastatic lymphadenopathy, with no other metabolically active foci. Lymph node dissection was performed, with two out of twenty-eight lymph nodes showing melanoma micrometastases. On follow-up exams, a mobile <1cm lymph node was noted on the left occipital scalp, which has been clinically stable. The patient's current staging is T4aN2bM0 (Stage III). However, repeat PET-CT from late October 2016 was concerning for progressing metastatic disease. Currently, various treatment options including chemotherapy and immunotherapy, in addition to excision of the remainder of the congenital melanocytic nevus, are in consideration.

DISCUSSION

Congenital melanocytic nevi (CMN) are present in 1-6% of neonates. They are more common in individuals with skin phototypes III-VI. CMN are commonly categorized according to size. The current classification system divides CMN into four categories based on the largest predicted diameter in adulthood. In this classification system, small CMN are defined as less than 1.5 cm in largest diameter; medium as 1.5-20 cm; large as 20-40 cm and giant as > 40 cm in diameter. Since CMN enlarge proportionally to a child's growth, a good rule of thumb for estimating the increase in diameter from infancy to adulthood is to multiply the size of lesions on the head of a newborn by a factor of two and those on other anatomic sites by a factor of three. Genetically, large and giant CMN exclusively harbor somatic gain-of-function mutations in *NRAS*, and the proportion of *BRAF* mutations increases with reduction in size of the CMN. On histopathology, when compared to acquired nevi, CMN demonstrate nevomelanocytes that tend to extend deeper into the dermis and subcutaneous tissue. These melanocytes often track along or within neurovascular and adnexal structures. The three major complications of CMN include melanoma, proliferative nodules and neurocutaneous melanosis (NCM). All three complications are most commonly associated with large and giant CMN.

NCM is a rare complication of CMN related to leptomeningeal and CNS melanosis. The risk of NCM is highest in those with CMN larger than 40 cm in final size, CMN located in the posterior axial position, patients with multiple satellite nevi, or individuals with numerous medium-sized CMN. Limited evidence suggests that approximately 1-10% of patients with evidence of NCM on imaging develop neurological symptoms such as developmental delay, seizures and hydrocephalus. Symptoms present at a median age of 2 years. The preferred imaging modality is MRI with gadolinium. The age at which imaging should be performed is controversial, but the traditional recommendation is six months of age. Prognosis in symptomatic patients is poor.

The lifetime risk of melanoma in small and medium-sized CMN is considered to be less than 1%. When melanoma does occur, it tends to present after puberty within the dermal-epidermal junction. For patients with large and giant CMN, the lifetime risk of developing cutaneous or extracutaneous melanoma is estimated to be between 2 and 5%, with greater than 50% of cases occurring within the first five years of life. Less than thirty cases of infantile (defined as diagnosed before the age of one) or congenital melanoma have been reported since 1925. Fifteen of these cases have been associated with CMN with the remainder classified as either *de novo* or from transplacental metastases. Given the high mortality associated with melanoma, it is critical to differentiate between malignant melanoma and proliferative nodules. Proliferative nodules are benign melanocytic proliferations, arising in congenital nevi in the newborn population with histologic and clinical appearance similar to that of a melanoma. Current evidence suggests that proliferative nodules are at least ten times more common than melanoma. As such, adjunctive studies including array comparative genomic hybridization (CGH) and FISH have been utilized to assist in differentiation. In general, segmental chromosomal aberrations have been observed in congenital melanomas.

There is limited evidence on the management of melanoma in the pediatric population. The majority of guidelines are derived from the adult literature. Generally, wide local excision is performed. As in adults, it is recommended that sentinel lymph node biopsy be performed in lesions with Breslow depth greater than 1 mm. There is very limited evidence on the use of adjuvant therapy in pediatric patients with stage III melanoma. The most commonly cited adjuvant therapy is Interferon-α2b. Options for children with distant metastases include enrollment in clinical trials and palliative radiation. Given the association with melanoma, close clinical follow-up of patients with large and giant CMN is recommended.

KEY POINTS

1. The three major complications of CMN are proliferative nodules, melanoma and neurocutaneous melanosis. All of these entities are most commonly seen with large and giant CMN.
2. Current evidence suggests that the lifetime risk of cutaneous or extracutaneous melanoma developing in association with a large or giant CMN is approximately 2-5%.
3. Three types of congenital melanoma exist: those associated with a congenital melanocytic nevus, *de novo* congenital melanoma, and transplacental metastasis. Less than 30 cases have been reported in the literature to date.
4. Differentiating between malignant melanoma and proliferative nodules arising in CMN in the newborn population is challenging and may require adjunctive modalities such as comparative genomic hybridization (CGH) and fluorescence *in situ* hybridization (FISH) to aid in diagnosis.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #4**

Presented by Kassandra Holzem, MD, Lauren Guggina, MD, and Jennifer Choi, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 77-year-old Caucasian male with chronic lymphocytic leukemia presented with a 3-month history of scattered cutaneous ulcerations. The lesions initially developed as multiple erythematous papules and nodules that subsequently ulcerated with purulent drainage. The patient reported mild associated pain without pruritus. Multiple skin biopsies and tissue cultures performed by outside providers were unrevealing. He had previously failed treatment with systemic corticosteroids, itraconazole, metronidazole, and piperacillin-tazobactam. He was subsequently transferred to Northwestern Memorial Hospital for further evaluation due to a 5-day history of declining mental status.

PAST MEDICAL HISTORY

Chronic lymphocytic leukemia, depression, gout, hyperlipidemia, hypertension, paroxysmal atrial fibrillation

MEDICATIONS

Allopurinol, colchicine, digoxin, escitalopram, ibrutinib

PHYSICAL EXAM

On the patient's face, trunk, and extremities, there were several scattered erythematous to violaceous fluctuant papulonodules and plaques ranging in size from 0.2 to 3 cm, as well as several eroded and verrucous erythematous to violaceous plaques.

LABS/IMAGING

Abnormal:

Labs: albumin 3.2 (ref. 3.5-5.7), quantitative IgG 388 (ref. 700-1600), quantitative IgA 58 (ref. 70-400)

MRI brain: well-circumscribed T1 hypointense and T2 isointense lesion in the posteromedial occipital lobe with peripheral enhancement and associated edema concerning for a cerebral abscess

Normal/Negative: CBC, BMP, AST, ALT, LDH, TSH, ACE, ANCA, quantitative IgM, T-cell monitoring panel, syphilis antibody, fungal blood culture, cutaneous gram stain, cutaneous bacterial culture, cutaneous fungal culture, cutaneous mycobacterial culture, EEG, and video EEG

HISTOPATHOLOGY

Outside surgical pathology interpretation: skin with suppurative periseptal and lobular panniculitis with scattered large cells with smudgy nuclei. Special stains, including DPAS, PAS, Giemsa, GMS, Gram, and AFB, were negative for microorganisms.

Dermatopathology interpretation: dermal abscess with tissue necrosis and large cells with smudgy nuclei and prominent nucleoli. Focal erythrophagocytosis was noted within these large cells. Special stains, including DPAS, PAS, Giemsa, GMS, Gram, and AFB, were negative for microorganisms.

Tissue PCR: *Acanthamoeba* spp.

DIAGNOSIS

Disseminated acanthamoebiasis

TREATMENT AND COURSE

Shortly after admission, tissue PCR results from a previously performed biopsy demonstrated *Acanthamoeba* spp. Empiric broad-spectrum antimicrobial therapy was initiated with clarithromycin, fluconazole, flucytosine, pentamidine, and sulfadiazine. The Centers for Disease Control and Prevention (CDC) was contacted, and miltefosine was added to the regimen. Despite aggressive management, the patient's mental status failed to improve, and he was ultimately discharged with hospice care.

DISCUSSION

Acanthamoeba is a free-living amoeba that is found worldwide in water and soil. It is a rare human pathogen and is one of only four such amoebae with the ability to cause disease. Infection with this organism typically affects the eye, nervous system, or skin and can lead to three main forms of illness, including *Acanthamoeba* keratitis, granulomatous amoebic encephalitis, and disseminated acanthamoebiasis.

Acanthamoeba keratitis most commonly occurs in healthy contact lens wearers due to poor contact lens hygiene. Though localized to the eyes, this form of disease can result in serious complications, including blindness. Granulomatous amoebic encephalitis (GAE) and disseminated acanthamoebiasis occur due to hematogenous spread following direct inoculation into broken skin or inhalation in an immunocompromised host. Mortality risk is high with disseminated disease and GAE.

Cutaneous disease can occur with disseminated acanthamoebiasis and GAE. Lesions are typically nonspecific, ulceronecrotic or verrucous plaques that may be painful or asymptomatic. The differential diagnosis is broad, and biopsy with tissue culture is essential to the diagnosis. Histopathologic evaluation reveals dense dermal histiocytic inflammation. Careful examination may reveal amoebic trophozoites within the infiltrate; however, these are frequently mistaken for histiocytes. Advanced techniques, such as PCR, should be employed if available.

No established treatment regimen for disseminated acanthamoebiasis exists. Miltefosine is a phosphocholine analogue that is available as an investigational drug from the CDC for treatment of infections due to free-living amoebae. Though the number of cases treated with a miltefosine-containing regimen is small, case series suggest a survival advantage. Clinicians caring for patients with suspected acanthamoebiasis should contact the CDC for guidance on diagnosis and management.

KEY POINTS

1. Disseminated acanthamoebiasis should be considered in the differential diagnosis of widespread cutaneous lesions that fail to respond to broad-spectrum antimicrobial agents.
2. Histopathologic diagnosis of *Acanthamoeba* infection is often difficult as amoebae are frequently misidentified as histiocytes. Tissue PCR should be employed if available.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #5**

Presented by Steve Xu, MD, MSc (Lond.), Michael W Pelster, MD, and Anne Laumann, MBChB/MRCP (UK)
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 58-year-old female presented with skin changes of the left breast present since her 20s that worsened after a lumpectomy 4 years prior.

CHICAGO DERMATOLOGICAL SOCIETY **Case #6**

Presented by Lida Zheng, MD[1] and Anthony J Mancini, MD[2]
[1]Department of Dermatology, Feinberg School of Medicine, Northwestern University
[2]Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 3-day-old female was born at 38 weeks gestation with a large facial mass and disseminated deep cutaneous red to blue nodules. There was no history of maternal infection, and routine prenatal serologies for infection were unremarkable. The infant was diagnosed prenatally with a facial mass. Fetal MRI revealed that the mass seemed to arise from the left frontal lobe through a defect in the cribriform plate. Apgar scores were 8 and 9 at one and five minutes, respectively.

PHYSICAL EXAM

Vitals: afebrile, weight 3.7 kg (8 lbs 2.5 oz), head circumference 42 cm (including head mass)
HEENT: see skin exam below, no corneal opacities, normal ears
Cardiovascular: regular rate and rhythm, no murmurs
Abdominal: soft, no masses, no appreciable hepatosplenomegaly
Neurological: alert, normal tone
Lymph nodes: no lymphadenopathy
Skin: On the superior half of the forehead was a large, firm, multilobulated, exophytic, erythematous tumor with foci of necrosis. Over the scalp, face, trunk and extremities were numerous, deep red to blue, infiltrative papules and papulonodules, several with central necrosis and crusting.

LABORATORY

Abnormal: PTT 48 (ref. 31.1-38.6)
Normal/Negative: CBC, PT/INR, BMP, LFTs. Blood cultures negative. Mother and infant both A+ blood type. Maternal prenatal serologies/testing reported negative (varicella, rubella, CMV, and toxoplasmosis).

IMAGING

MRI Head/Brain: 4.5 x 7.0 x 10.3 cm facial mass with a thick peripheral-enhancing nodular component and central cystic necrosis without evidence of intracranial extension. Numerous enhancing nodules throughout the scalp, superficial and deep neck and visualized chest wall, mediastinum and upper extremities. Unremarkable MRI appearance of the brain, with no evidence of intracranial extension.

HISTOPATHOLOGY

Proliferation of undifferentiated small round blue cells with scant cytoplasm, hyperchromatic nuclei and prominent eosinophilic nucleoli infiltrating through the dermis and subcutaneous tissue. Mild pleomorphism was noted. Rare multinucleated giant tumor cells were noted as well as numerous apoptotic bodies and mitotic figures. Tumor cells stained strongly positive for desmin, myogenin, and myoD1. Sampled specimen was negative for PAX3-FOXO1 and PAX7-FOXO1 fusion transcripts by RT-PCR.

DIAGNOSIS

Congenital metastatic rhabdomyosarcoma, suspect alveolar subtype

TREATMENT AND COURSE

The patient's lesions rapidly enlarged in size and number. Further imaging also showed suspicious lesions of the paraspinal muscles, retroperitoneum, pancreas, splenic hilum, and hepatorenal fossa. She developed significant respiratory distress related to airway obstruction and was treated with non-invasive ventilatory support. Given the poorly differentiated nature of her tumor, limited reported responses of metastatic disease to chemotherapy, poor candidacy for surgical intervention, and multiple discussions with the family, the decision was made to pursue palliative care. The patient died at 17 days of age.

DISCUSSION

Rhabdomyosarcomas (RMS) are primitive mesenchymal cell-derived tumors of striated muscle origin which represent approximately 3-4% of all childhood cancers. Although uncommon, they make up half of all pediatric soft tissue sarcomas. The majority of RMS present in childhood, typically between the ages of 2-6 years. Only 1-2% of RMS are congenital, and 5-10% occur prior to age 1. The most common primary sites are the head and neck, genitourinary tract, and the extremities. The primary symptoms usually relate to mass effect on the affected region. There are several subtypes of RMS: alveolar (the suspected subtype in this case), embryonic (including the botryoid variant), and anaplastic (formerly called pleomorphic). RMS may occasionally be associated with neurofibromatosis type 1, Li-Fraumeni syndrome, Noonan syndrome, Beckwith-Wiedemann syndrome and Costello syndrome. Notably, patients with neurofibromatosis type 1 have a 20-fold increased risk of RMS.

Histologic evaluation is required for diagnosis. Pathology reveals small, round, blue cells that stain positively for desmin, myogenin, and/or myoD1. Of the histological subtypes, the alveolar subtype shows stronger myogenin and myoD1 staining. The alveolar subtype represents 20-30% of RMS, and a substantial proportion (25-30%) present with metastatic disease. Alveolar subtype RMS also characteristically exhibit a chromosomal translocation of t(2;13) or t(1;13) to generate a fusion gene of PAX3 or PAX7 and FOXO1; however, 20% are fusion gene negative.

Multidisciplinary treatment protocols (surgery, radiation, and chemotherapy) have improved the outcome of children with RMS over the last 30 years. The 5-year survival rate has improved from 53% in 1975 to 67% in 2010. Patients are stratified into risk groups to guide treatment, which is determined by stage, site, size, the age of the patient, and histology.

Neonatal RMS is particularly challenging, especially if local control via surgical resection is not feasible. Both ages <1 year and > 10 years have been independently associated with a poorer prognosis. Metastasis, alveolar subtype, and ulceration of lesions (indicating rapid growth) are also associated with a worse prognosis. Favored sites of metastatic spread are the lungs, followed by the bone marrow, lymph node and bones. The 5-year event-free survival of patients with alveolar subtype is 40%, compared to 70% for the embryonic subtype. Increased rate of metastases is thought to contribute to the worse prognosis seen with alveolar subtype RMS.

The differential diagnosis of congenital RMS with cutaneous metastases mirrors that of a "blueberry muffin" baby, the description classically applied to newborns presenting with diffuse violaceous to blue, non-blanching papules and nodules secondary to extramedullary hematopoiesis or a diffusely metastatic malignancy. Infectious etiologies include neonatal toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, and Epstein Barr virus. Malignancies that may present in this fashion include cutaneous metastases from neuroblastoma, leukemia, and sarcomas like RMS. Blueberry muffin lesions can also be seen in primary disorders of red blood cells, including erythroblastosis fetalis and in patients with Langerhans cell histiocytosis. Additional diagnostic considerations include multifocal lymphoangioendotheliomatosis with thrombocytopenia and blue rubber bleb nevus syndrome. In a study examining post-mortem

cutaneous metastases of non-hematopoietic cancers, the most likely pediatric tumors to metastasize to the skin were RMS and neuroblastoma, both of which are more likely than their adult counterparts to disseminate to multiple cutaneous sites.

KEY POINTS

1. Pediatric rhabdomyosarcoma is an aggressive soft tissue sarcoma that can rarely present with localized skin involvement or disseminated cutaneous metastases.
2. The congenital alveolar subtype of pediatric RMS is an extremely aggressive form of this tumor, with few long-term survivors.
3. The newborn baby presenting with multiple red or blue cutaneous nodules ("blueberry muffin" baby) merits prompt evaluation with skin biopsy and consideration of a variety of infectious and neoplastic disorders.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #7**

Presented by Elisha Singer, MD, Sarah Adams, MD, and Jennifer Choi, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 60-year-old female with a history of a malignant islet cell tumor of the pancreas was referred for evaluation of a cutaneous eruption of eight months duration. She described the eruption as pruritic, inflamed, and at times oozing and painful. Initially located on her bilateral legs, the eruption subsequently spread to her bilateral thighs, elbows, and ultimately the perianal and genital skin. She also complained of dry, cracked lips at the corners of her mouth. Previous transiently successful treatments included intramuscular triamcinolone acetonide and a methylprednisolone dose pack. On review of systems, the patient noted a six-pound weight loss over the preceding four months; she denied fevers, fatigue, drenching night sweats, diarrhea or joint pains.

PAST MEDICAL HISTORY

Malignant islet cell tumor of the tail of the pancreas s/p distal pancreatectomy and splenectomy, followed by recurrent metastatic disease to liver and peri-aortic lymph nodes
Ductal carcinoma in situ of the right breast s/p right mastectomy and tamoxifen therapy
DVT/PE
Supraventricular tachycardia
Type 2 diabetes mellitus
Hypothyroidism

MEDICATIONS

Enoxaparin, diltiazem, levothyroxine, insulin glargine, glipizide, prochlorperazine

SOCIAL HISTORY

Married with two children. Denied tobacco, alcohol or drug use.

PHYSICAL EXAM

The patient was a well-appearing female in no acute distress. The extensor surfaces of the thighs and legs, as well as the perianal and genital region were noted to have erythematous patches and thin plaques with overlying exfoliative, "flaky-paint" scale. There were thin fissures at the lateral commissures of the mouth. No cervical, axillary or inguinal lymphadenopathy was palpable.

LABS

Abnormal: glucose 329, chromogranin A 119 (ref. <15), glucagon 618 (ref. <134)
Normal/Negative: vitamin B1, vitamin B6, vitamin B12

HISTOPATHOLOGY

The epidermal surface revealed a layer of epidermal necrosis with parakeratotic strands. Beneath this, there was underlying orthokeratosis, a reactive epidermis, and scattered necrotic cells.

DIAGNOSIS

Necrolytic migratory erythema

TREATMENT AND COURSE

The patient's necrolytic migratory erythema was successfully controlled with 20 mg of prednisone daily for two weeks. However, upon discontinuation, she developed recrudescence of her cutaneous eruption necessitating chronic, low-dose steroid therapy with prednisone 10 mg daily, which led to significant control of her skin disease. Her malignant islet cell tumor was initially treated with long-acting octreotide followed by radioembolization therapy to her liver metastases; however, given progression of her disease, she was transitioned to everolimus. She subsequently developed new metastatic disease to her T9 vertebral body and was therefore started on sunitinib malate, but given intolerance to this, she was switched to capecitabine and temozolomide chemotherapy.

DISCUSSION

Necrolytic migratory erythema (NME) is a rare paraneoplastic condition that is the presenting manifestation of glucagonoma syndrome in 70% of affected patients. Becker et al. first reported this condition in 1942 in a patient with pancreatic cancer that developed an erythematous vesicular eruption. In 1973, Wilkinson et al. named this condition necrolytic migratory erythema.

Glucagonomas are rare neuroendocrine pancreatic tumors with an estimated incidence of one in 20 million. They most often occur in individuals 40 to 70 years old and are primarily located in the body or tail of the pancreas. Glucagonoma syndrome, in addition to NME, also includes glucose intolerance, weight loss, anemia, aminoaciduria, venous thromboembolic disease, psychiatric disturbances, and increased glucagon levels.

NME is characterized by a pruritic and recalcitrant dermatitis. The lesions consist of erythematous, crusted plaques most often located in the genital and perianal region, lower extremities, and at times the trunk or upper extremities. Additionally, there may be associated angular stomatitis and glossitis. NME is characterized by periods of spontaneous exacerbation and remission.

There are several theories regarding the underlying pathophysiology of NME. Reports indicate that hyperglucagonemia causes increased hepatocyte gluconeogenesis and lipolysis, ultimately leading to hypoaminoacidemia. Elevated glucagon levels also stimulate the production of arachidonic acid, prostaglandins, and leukotrienes, which are thought to contribute to the inflammatory reaction in NME. The fact that NME often clears with medications that suppress glucagon levels supports the central role of hyperglucagonemia. In addition to glucagon's role, many patients with NME have underlying deficiencies of zinc, protein, amino acids, and essential fatty acids, and reports indicate that supplementation of these nutrients may lead to clearance of NME.

Diagnosis of NME is often challenging, as the skin lesions often mimic other dermatoses including atopic dermatitis, seborrheic dermatitis, psoriasis, pemphigus vulgaris, candidiasis, and nutritional deficiencies. Histological analysis characteristically reveals epidermal pallor, spongiosis, and necrotic keratinoctyes. A perivascular infiltrate of lymphocytes and histiocytes may also be seen. Laboratory analysis reveals elevated serum glucose, glucagon, and chromogranin, as well as a normochromic normocytic anemia. The serum zinc level is often decreased as well. Pancreatic tumors can be visualized with computer tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), or pancreatic arterial angiography.

Surgical removal of the pancreatic tumor is the definitive treatment for glucagonoma syndrome. However, surgical removal is not always feasible given that at least 50% of well-differentiated glucagonomas have metastasized at the time of diagnosis. Medical therapies include octreotide (a somatostatin analogue), everolimus (an mTOR inhibitor), sunitinib (a tyrosine kinase

inhibitor), and standard chemotherapeutic agents. Recently, reports indicate that repletion of amino acids, essential fatty acids, and zinc also may also be effective treatment modalities.

To date, there are no reports of systemic corticosteroid therapy as an effective treatment for NME. Though use of topical clobetasol propionate 0.05% for NME has been reported in the literature, the case report was confounded by the concomitant use of systemic octreotide. Furthermore, our patient did not respond to topical treatment with halobetasol propionate 0.05% ointment alone, suggesting that systemic steroid therapy may be more effective than topical therapy. As corticosteroids are known to inhibit production of phospholipase A2 and thus epidermal arachidonic acid, there is pathophysiological rationale for the efficacy of corticosteroid therapy in NME. This case supports the use of systemic corticosteroids as an adjunctive therapy in patients with treatment-refractory NME.

KEY POINTS

1. NME is characterized by a pruritic and recalcitrant dermatitis with lesions most often located in the genital and perianal region, lower extremities, and at times the trunk or upper extremities, with periods of spontaneous exacerbation and remission.
2. Diagnosis of NME is challenging as skin lesions often mimic other dermatoses including atopic dermatitis, seborrheic dermatitis, psoriasis, pemphigus vulgaris, candidiasis, and nutritional deficiencies.
3. Laboratory analysis commonly reveals elevated serum glucose, glucagon, and chromogranin, as well as a normochromic normocytic anemia.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #8**

Presented by Joshua Owen, MD, PhD[1] and Anthony J Mancini, MD[2]
[1]Department of Dermatology, Feinberg School of Medicine, Northwestern University
[2]Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 28-day-old infant presented with a spreading bullous skin eruption, tachycardia, and low-grade fever.

CHICAGO DERMATOLOGICAL SOCIETY **Case #9**

Presented by Betty Kong, MD, PhD, Kassandra Holzem, MD and Emily Keimig, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
A 42-year-old male presented with a several month history of erythematous scaling plaques on the lower extremities. He was initially diagnosed with asteatotic eczema and was given instructions for dry skin care. He returned two months later with a worsening ichthyosiform eruption and significant lower extremity edema. At that time, he also endorsed fatigue, weight loss, fevers, and night sweats.

One year prior, the patient had developed erythema nodosum-like lesions following an episode of streptococcal pharyngitis confirmed by elevated anti-streptolysin O (ASO) titers. These lesions spontaneously resolved.

PAST MEDICAL HISTORY
None

MEDICATIONS
None

SOCIAL HISTORY
Works as a firefighter

PHYSICAL EXAM
Upper extremities with scaly, erythematous, annular thin plaques. Lower extremities with non-pitting edema extending to the mid thighs with overlying ill-defined erythematous scaly patches, some of which had scattered heme-crusted erosions and ulcerations.

LABS/IMAGING
Abnormal:
Labs: WBC 1.5 (absolute neutrophil count: 0.8, absolute lymphocyte count: 0.7), Hgb 13.0, platelets 116 (ref. 150-400), ALT 114 (ref. 8-40), AST 129 (ref. 8-40), ferritin 2945 (ref. 24-336), LDH 654 (ref.140-280), angiotensin-converting enzyme (ACE) 169 (ref. 9-67)
CT chest/abdomen/pelvis: mild diffuse bronchial wall thickening; non-calcified pulmonary nodules in the right lower lobe; mild hepatosplenomegaly; mildly enlarged lymph nodes in the axillary and external iliac chains
Bone marrow biopsy: hypercellular bone marrow with granulocytic hyperplasia and scattered non-caseating granulomas; fungal and AFB stains negative; CMV PCR negative

Normal/Negative: calcium, HIV, parvovirus IgM, CMV IgM, EBV IgM, hepatitis serologies, QuantiFERON gold, blood cultures, *Histoplasma* urine antigen, *Blastomyces* urine antigen, ANA, anti-mitochondria antibody (AMA), ANCA, alpha-fetoprotein (AFP), peripheral flow cytometry, transthoracic echocardiogram

HISTOPATHOLOGY
Granulomatous lobular panniculitis. Stains for fungi, bacteria, and acid fast bacilli were negative.

DIAGNOSIS
Subcutaneous sarcoidosis, Darier-Roussy subtype

TREATMENT AND COURSE

The patient was started on prednisone 20 mg daily. This was increased to 40 mg daily due to worsening swelling and evolving lesions on the arms and legs. Methotrexate has been considered as a steroid-sparing agent; however, it has been deferred given his elevated transaminases pending further evaluation by hepatology. He is also being evaluated by pulmonology, rheumatology, and hematology/oncology.

DISCUSSION

Sarcoidosis is a systemic granulomatous disorder of unknown etiology. It most commonly involves the lungs but can involve essentially every organ system, including the skin. Its cutaneous manifestations can be diverse, nonspecific, and protean. Therefore, it is a diagnosis of exclusion requiring negative workup for autoimmune, infectious, and neoplastic etiologies.

Cutaneous manifestations are seen in up to one third of patients and may be the first presentation of the disease. A variety of morphologies have been described, including papular (most common), annular, hypopigmented, plaque, erythrodermic, ichthyosiform, morpheaform, lupus pernio, and subcutaneous (Darier-Roussy) variants. Additionally, erythema nodosum is the most common nonspecific cutaneous finding in sarcoidosis and is associated with a good prognosis.

The classic presentation of subcutaneous sarcoidosis includes painless, firm, mobile nodules, representing disease infiltration of the subcutaneous tissue. The overlying epidermis may be normal, erythematous, or violaceous. The upper extremity is the most frequently affected area, and facial involvement is rare. About 90% of patients will have systemic involvement, but the overall prognosis is good.

Of note, our patient is a firefighter, one of several occupations in which environmental exposures have been implicated in the pathogenesis of sarcoidosis. Indeed, several studies have reported an increased incidence of sarcoidosis among first responders after the World Trade Center attacks on September 11, 2001. Other occupational risks associated with the development of sarcoidosis include employment in the agriculture sector and/or exposures to insecticides and microbial bioaerosols.

KEY POINTS

1. Sarcoidosis is a granulomatous condition of unknown etiology that can present with a myriad of systemic findings. Diagnosis requires exclusion of infectious and autoimmune etiologies.
2. Darier-Roussy sarcoidosis is a rare variant of sarcoidosis that presents with subcutaneous nodules.
3. An erythema nodosum-like eruption should prompt a workup for associated conditions, including sarcoidosis.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #10**

Presented by Joel Sunshine, MD, PhD and Ahmad Amin, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
A 53-year-old Caucasian male presented with a mass on the left upper arm. He had first noted the mass one month prior to presentation and reported a relatively stable appearance outside of it becoming more "bruised" over time. He denied any associated pain, pruritus, preceding trauma, recent illnesses, fevers, chills, weight loss, or night sweats.

PAST MEDICAL HISTORY
GERD, scoliosis, hyperlipidemia

MEDICATIONS
Pantoprazole

FAMILY HISTORY
Father with melanoma

PHYSICAL EXAM
Left upper arm: A 3 x 2 cm firm, mobile, subcutaneous mass that was warm to touch with overlying erythema and fine vessels.

LABS/IMAGING
Ultrasound of the left upper extremity showed a 3.1 x 1.0 x 2.5 cm lobulated hypoechoic mass in the subcutaneous fat with multiple internal septations and prominent vascularity.

HISTOPATHOLOGY
Incisional biopsy showed a deep dermal tumor arranged in a trabecular pattern with no connection to the dermoepidermal junction. The tumor was composed of sheets of uniform small cells with high nuclear to cytoplasmic ratio, nuclei with dense chromatin and small nucleoli, numerous mitotic figures, and apoptotic cells. Focal areas of necrosis and pseudorosette formation were noted. The dermis also showed a variable, mostly perivascular, lymphohistiocytic infiltrate. Immunohistochemistry was positive for polyomavirus, synaptophysin, and cytokeratin (AE1/3, with a dot-like pattern) and was negative for vimentin and chromogranin.

DIAGNOSIS
Merkel cell carcinoma (MCC)

TREATMENT AND COURSE
The patient was referred to surgical oncology for wide local excision and sentinel lymph node biopsy. Preoperative MRI of the humerus showed the tumor abutting the fascia of the triceps, but there was no abnormality or enhancement within the muscle. PET/CT showed no evidence of metastatic disease. Merkel cell polyomavirus antibody titer was 1330. The re-excision specimen was clear of any involvement, and sentinel lymph node biopsy was negative for carcinoma. The patient will be followed closely at 3-month intervals with plans to monitor the Merkel cell polyomavirus titer and to perform surveillance chest X-ray and ultrasound of the left upper extremity.

DISCUSSION
MCC predominantly affects older patients with lower Fitzpatrick phototypes, most often on sun-exposed areas of the head, neck, and extremities. It carries a disease-related mortality of 30% at 2

years and 50% at 5 years after diagnosis. MCC usually presents as a rapidly growing, asymptomatic, reddish-blue dermal papule or nodule that develops over the course of weeks to months. Many patients present with metastatic disease, and there is a high risk of local, regional, and distant recurrences despite treatment.

There are three main risk factors associated with the development of MCC – ultraviolet radiation, immunosuppression, and the Merkel cell polyomavirus (MCPyV). Approximately 80% of all MCCs are associated with MCPyV, whose large T antigen inactivates p53 and retinoblastoma (Rb) proteins. Patients with MCPyV-positive tumors often produce virus-specific T cells and antibodies, which can be monitored during the disease course. MCPyV-positive tumors show strikingly low mutational burdens, especially when compared to UV-induced, MCPyV-negative MCCs, which are characterized by a greater than 100-fold higher mutational burden. Immunosuppressed patients, particularly solid organ transplant recipients and patients with B-cell lymphoma, show increased MCC incidence.

Patients who present with localized disease are staged using PET/CT and MRI. They are treated with complete resection of the primary tumor and SLN biopsy. They are also considered for adjuvant radiation therapy to the local lymph node basin, which is associated with improved overall survival in stage I or II MCC (localized, clinically node-negative disease, with primary tumor size < 2 cm or > 2cm, respectively).

Until recently, options for treatment of advanced MCC (stage III/IV) were limited. Cytotoxic chemotherapy, while frequently inducing temporary responses, offers a median progression-free survival of only 3 months and is not associated with an improved overall survival compared to surgical resection alone. Several recent trials using programmed cell death protein 1 (PD-1)-directed immune checkpoint inhibitors have shown substantial promise. A recent phase II study of pembrolizumab, an anti-PD-1 antibody, in 26 patients with advanced MCC showed objective responses in 14/25 (56%) patients, with 4 complete responders (CRs) and 10 partial responders (PRs). With a median follow-up of 33 weeks, only 2 of 14 patients had relapsed. Six-month progression-free survival was 67%. Importantly, both MCPyV-positive and negative patients showed responses to pembrolizumab, with 62% and 50% response rates, respectively. Another phase II trial with avelumab, an anti-programmed death ligand (PD-L1) antibody, in patients with MCC refractory to chemotherapy, showed objective responses in 28/88 (31.8%) patients, including 8 CRs and 20 PRs, with maintenance of response in the majority (23/28 or 82%) of patients.

KEY POINTS

1. MCC is a rare but aggressive skin cancer. Localized disease is treated with surgical resection and/or radiation but has a high rate of local, regional, and distant recurrences.
2. PD-1 pathway checkpoint inhibitors have shown substantial promise for patients with advanced MCC.

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