Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, November 8, 2017
Gleacher Center – Chicago, IL

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

Program

Host: Northwestern University
Wednesday, November 8, 2017
Gleacher Center, Chicago

8:00 a.m.	**Registration & Continental Breakfast with Exhibitors** *All activities will take place on the 6th Floor of the Gleacher Center*
9:00 a.m. - 10:30 a.m.	**Clinical Rounds** Slide viewing/posters Patient viewing
9:00 a.m. - 10:00 a.m.	**Basic Science/Residents Lecture** "Why Do Viruses Cause Cancer" *Patrick S. Moore, MD, MPH*
10:00 a.m. - 10:30 a.m.	**Break and Visit with Exhibitors**
10:30 a.m. - 12:15 p.m.	**Resident Case Presentations & Discussion;** **MOC Self-Assessment Questions**
12:15 p.m. - 12:45 p.m.	**Box Lunches & visit with exhibitors**
12:55 p.m. - 1:00 p.m.	**CDS Business Meeting**
1:00 p.m. - 2:00 p.m.	**General Session** BLUEFARB LECTURE - "Skin Cancers and Viruses: Lessons from Kaposi's Sarcoma and Merkel Cell Carcinoma" *Patrick S. Moore, MD, MPH*
2:00 p.m.	**Meeting adjourns**

Mark the Date!
Next CDS monthly meeting – Hosted by the University of Chicago
Wednesday, December 13th; Gleacher Center, Chicago

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

Guest Speaker

PATRICK S. MOORE, MD, MPH

Professor, Department of Molecular Genetics and Biochemistry, University of Pittsburgh School of Medicine; Leader of the Cancer Virology Program at the University of Pittsburgh Cancer Institute Pittsburgh, PA

Patrick S. Moore, MD, MPH is an American Cancer Society (ACS) Professor in the Department of Microbiology and Molecular Genetics, University of Pittsburgh. He is Director of the Cancer Virology Program for the University of Pittsburgh Cancer Institute. Dr. Moore is recognized for his role, together with Dr. Yuan Chang – also an ACS Professor – in discovering and characterizing Kaposi sarcoma herpesvirus (KSHV or HHV8) and Merkel cell polyomavirus (MCV), the two most recently recognized human tumor viruses. Drs. Moore and Chang's laboratory maintain an active focus on basic and translational research for both KSHV and MCV. Dr. Moore has received the General Motors Cancer Research Foundation Mott Award, the Robert Koch Prize, the Meyenburg Cancer Research Prize as well as other awards, and 21 patents. He is a Thomson Reuter ISI Highly Cited Researcher with over 12,000 scientific citations since 1992. Dr. Moore received medical and graduate degrees from the University of Utah, Stanford University and University California, Berkeley and trained at the Centers for Disease Control as an Epidemic Intelligence Service (EIS) officer.

CME Information

This educational activity is jointly provided by the Chicago Dermatological Society in partnership with the Indiana Academy of Ophthalmology

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 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 2017/18 series of meetings, the participant should be able to:

1. Discuss key factors in the diagnosis and treatment for allergic conditions, 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 Indiana Academy of Ophthalmology (IAO) and the Chicago Dermatological Society. IAO is accredited by the Indiana State Medical Association to provide continuing education for physicians.

Credit Designation for Physicians – IAO designates this live activity for a maximum of 4.5 *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 evaluation form, at the registration table when you leave the meeting. Thank you for your attention to this important item. Note - You may complete the paper version of the evaluation form or submit your evaluation online.

Disclosure of Conflicts of Interest

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

The guest speaker's disclosure will be made at the meeting. None of the planning committee members have any conflicts of interest to disclose.

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Contact Information

For information about the physician accreditation of this program please contact the CDS administrative office at: 847-680-1666; email: Rich@RichardPaulAssociates.com

Americans with Disabilities Act

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

Disclaimer

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

Dislosure of Unlabeled Use

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

NORTHWESTERN UNIVERSITY
FEINBERG SCHOOL OF MEDICINE
DEPARTMENT OF DERMATOLOGY

DERMATOLOGY RESIDENTS

Third Year
Amin Esfahani, MD, MSc
Kassandra Holzem, MD
Sreya Talasila, MD
Steve Xu, MD, MSc (Lond.)

Second Year
Brittany Dulmage, MD
Betty Kong, MD, PhD
Joshua Owen, MD, PhD
Joel Sunshine, MD, PhD

First Year
Raj Chovatiya, MD, PhD
Julia Mhlaba, MD
Olivia Schenck, MD
Jennifer Shastry, MD

Medicine-Dermatology
Elisha Singer, MD (PGY-5)
Namita Jain, MD, MPH (PGY-4)
Lida Zheng, MD (PGY-3)
Andrew Para, MD (PGY-3)

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CHICAGO DERMATOLOGICAL SOCIETY **Case 1**

Presented by Brittany Dulmage, MD and Joan Guitart, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 52-year-old Hispanic female presented to Northwestern Memorial Hospital's inpatient hematology/oncology service for work-up of hemophagocytic lymphohistiocytosis and on arrival reported painful lesions on her legs and trunk evolving over the previous four months. Four months prior to presentation, she developed erythematous painful and occasionally pruritic nodules on her shins and right calf. Two months prior to presentation, she was started on prednisone 40mg daily and diflorasone ointment with some improvement in her skin lesions. One month prior to presentation, she developed new erythematous lesions on her bilateral breasts and forearms, which were pruritic and painful.

In addition to her skin findings, she endorsed a three month history of new-onset right upper quadrant pain which had been evaluated by ERCP which showed possible primary sclerosing cholangitis and liver biopsy which revealed a marked histiocytic infiltrate in the sinusoids and minimal macrovesicular fatty change concerning for hemophagocytic lymphohistiocytosis. This right upper quadrant pain continued, and she also developed new fevers, dry cough, and dyspnea, ultimately prompting her admission to an outside hospital for community acquired pneumonia and subsequent transfer to Northwestern. She also endorsed a thirty-pound weight loss in four months, as well as fatigue, chills, drenching night sweats, and lumps in the bilateral axillae.

PAST MEDICAL HISTORY

Hypertension, hyperlipidemia, type 2 diabetes mellitus, depression

PAST SURGICAL HISTORY

Cholecystectomy

FAMILY AND SOCIAL HISTORY

The patient had an extensive family history of breast and ovarian cancer with several siblings BRCA+; she had been tested for BRCA mutations and was negative. Married with four children; one died at the time of childbirth. No smoking or alcohol use. She worked at a factory, was born in Mexico, and last traveled there in 2015.

MEDICATIONS

Acetaminophen/hydrocodone, pravastatin, carvedilol, metformin, glimepiride, diflorasone ointment, saxagliptin, bupropion, paroxetine, prednisone, pantoprazole

PHYSICAL EXAM

Central forehead with a subtle slightly erythematous indurated plaque. Right breast with erythematous indurated plaques in a reticular pattern with slightly accentuated borders, blanchable, no scaling. Bilateral forearms with erythematous indurated plaques, some with suggestion of reticular configuration, no scaling. Bilateral shins, R>L with red brown patches and thin plaques. R calf with one ill-defined subcutaneous nodule. No palpable cervical, axillary, or inguinal lymphadenopathy.

LABS/IMAGING

Abnormal:

Labs: Ferritin 1495 (ref 11-307 ng/mL), EBV qPCR 270,000 IU/mL, platelet count 85 (ref 140-390 K/UL), ALT 387 (ref 0-52 U/L), AST 211 (ref 0-39 U/L), total bilirubin 3.36 (ref 0.0-1.0), direct bilirubin 2.1 (ref 0.0-0.2), fibrinogen 176 (ref 200-393 mg/dL), albumin 2.4 (ref 3.5-5.7 g/dL), protein 5.9 (ref 6.4-8.9 g/dL), triglycerides 267 (optimal <100)

Bone marrow biopsy: EBV+ T-cell lymphoproliferative disease with hemophagocytosis of red blood cells, neutrophils, platelets and lymphocytes. An abnormal T cell infiltrate involving ~10-20% of the bone marrow consisting of small- to medium-sized cells with somewhat irregular nuclei and with various degrees of loss of CD2, CD5, and CD7 was noted. EBER highlighted ~10% of the bone marrow cellularity.

PET/CT scan: Diffuse abnormal FDG hypermetabolism with innumerable cutaneous, subcutaneous and soft tissue attenuation nodules in the whole body as well as foci throughout almost the entire skeleton, activity in the liver, spleen, pancreas, and adrenals.

Normal/Negative: WBC

HISTOPATHOLOGY

Atypical lymphocytic infiltrate consistent with EBV-positive T-cell lymphoma with gamma-delta phenotype. The tumor cells were positive for CD3, CD4, TIA-1, gamma-M1 and delta TCR and negative for CD2, CD5, CD8, CD20, CD30, CD56 and BF1. EBV-encoded small RNA-1 in situ hybridization was positive for Epstein-Barr mRNA. Angiotropism or vasculitis was not noted.

DIAGNOSIS

EBV+ peripheral T-cell lymphoma with cutaneous involvement complicated by hemophagocytic lymphohistiocytosis

TREATMENT AND COURSE

The patient underwent four cycles of CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone) chemotherapy in preparation for planned allogeneic stem cell transplant. She was discharged briefly. However, she subsequently developed new fevers, worsening transaminitis, and hyperbilirubinemia thought to be due to lymphoma infiltration of liver or recurrence of hemophagocytic lymphohistiocytosis requiring readmission. Her course was complicated by severe metabolic acidosis ultimately requiring ICU transfer and intubation. She decompensated further, was extubated and placed on comfort care measures, and ultimately passed away two months after her initial hospital transfer.

DISCUSSION

Epstein-Barr virus (EBV) is a member of the herpesvirus family. Products of the EBV genome interact with or exhibit homology to a wide variety of human antiapoptotic molecules and cytokines hence promoting EBV infection, immortalization, and transformation. Most commonly, EBV infects B-cells first resulting in infectious mononucleosis and later persisting for the host's lifetime as a harmless passenger. However, in rare instances, EBV can transform B-cells producing B-cell lymphoproliferative disorders including EBV-related Burkitt's lymphoma. EBV can also infect T-cells leading to lymphoproliferative disorders including classic Hodgkin's lymphoma and T-cell non-Hodgkin's lymphomas including peripheral T-cell lymphomas, angioimmunoblastic T-cell lymphoma (AILT), extranodal nasal type NK/T-cell lymphoma, enteropathy-type T-cell lymphoma, gamma/delta T-cell lymphomas, EBV-associated cutaneous T-cell lymphoproliferative disorders (especially in Asia), and aggressive NK-cell leukemia/lymphoma.

Hemophagocytic lymphohistiocytosis (HLH) occurs in the setting of uncontrolled immune activation and is reflected in lab values, which show a state of extreme inflammation. HLH can be familial or occur secondary to infection, rheumatologic crisis, malignancy, or metabolic conditions. The most common causes of infectious HLH are EBV, cytomegalovirus, parvovirus B19, and HIV. Prompt recognition of HLH is extremely important, as the disorder is frequently fatal.

Diagnostic criteria for HLH per the HLH-2004 trial are 1) molecular identification of an HLH-associated gene mutation (including BIRC4, HPS, ITK, LYST, PRF1, Rab27A, SH2D1A, SLC7A7, STX11, STXBP2, UNC13D, XMEN) or 2) five of the eight following findings: fever > 38.5°C, splenomegaly, peripheral cytopenia, hypertriglyceridemia > 265 mg/dL fasting and/or hypofibrinogenemia < 150 mg/dL, hemophagocytosis in bone marrow, spleen, liver, or lymph nodes, low or absent NK cell function, ferritin > 500 ng/ml, and elevated soluble CD25. Of note, at the time of presentation, our patient met or nearly met five clinical criteria.

The diagnostic criteria developed under the HLH-2004 trial have come under some scrutiny as they were developed to diagnose primary or familial HLH in the pediatric population and perform less well in acquired or secondary forms of HLH in adult populations. As a result, the H-score was developed which uses weighted criteria, allowing more effective estimation of the individual's risk of having HLH. The total number of possible points in the H-score calculation is 337, and an H-score cutoff of 141 confers 100% sensitivity and 88% specificity. For adults, it is most effective when calculated at the time of presentation. There is an online tool available for easy calculation (http://saintantoine.aphp.fr/score/). On admission to Northwestern, our patient's H-score was 167.

The overall goal of HLH treatment is to halt any underlying trigger and control the immune system. Malignancy or infection should be treated immediately. In cases of lymphoma-associated HLH, a chemotherapy regimen containing etoposide should be started. Refractory or relapsed disease should be treated with allogeneic stem cell transplant.

KEY POINTS

1. EBV infection can lead to B-cell or T-cell lymphoproliferative disorders including leukemias and lymphomas with skin findings.
2. Hemophagocytic lymphohistiocytosis is a state of extreme uncontrolled immune activation with high fatality rates.
3. The H-score is a validated tool, which allows for determination of a patient's risk for HLH.

REFERENCES

1. Carbone A, et al. EBV-Associated Lymphoproliferative Disorders: Classification and Treatment. The Oncologist. 2009. 13(5):577-85.
2. Debaugnies F, et al. Performances of the H-Score for Diagnosis of Hemophagocytic Lymphohistiocytosis in Adult and Pediatric Patients. Am J Clin Pathol. 2016. 145(6):862-70.
3. Schram AM, et al. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood. 2015. 125(19):2908-14.

CHICAGO DERMATOLOGICAL SOCIETY **Case 2**

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

HISTORY OF PRESENT ILLNESS

A 20-day-old female born at 30-5/7 weeks gestational age (wga) by C-section due to preterm premature rupture of membranes/intrauterine growth restriction (PPROM/IUGR) and breech position presented with multiple birth defects. She was born to a primigravid mother with no significant past medical history and routine prenatal care. Her pregnancy course was significant for preeclampsia and maternal cholestasis of pregnancy. Maternal testing did not show evidence of trisomy 13, 18, or 21, and prenatal labs did not show evidence of infection with HIV, hepatitis B, or syphilis. During antenatal screening, the patient was found to have micrognathia and IUGR. At birth, she was intubated due to respiratory distress and remained ventilator-dependent with parenteral nutritional support until day 18 of life, when she was transferred to Ann & Robert H. Lurie Children's Hospital for further evaluation and management of multiple birth defects.

PAST MEDICAL HISTORY

Born at 30-5/7 WGA by C-section due to PPROM/IUGR and breech position

SOCIAL HISTORY

Born to Lithuanian parents with no known history of consanguinity

MEDICATIONS

Fentanyl, cefazolin, Total Parenteral Nutrition

PHYSICAL EXAM

Vital Signs: BP 78/47mmHg; Pulse 167; Temp 36.5 °C; Resp 58; Ht 36 cm; Wt 1.3 kg; HC 30 cm; SpO2 91%
General: Intubated and sedated.
Skin: Markedly dysmorphic facial features with tiny pinched nose, micrognathia, hypertelorism, and low set ears. Marked ectropion with chemosis of bilateral eyes. Unable to retract lids or examine globes. Large anterior fontanelle. Taut indurated shiny skin throughout with prominent superficial vasculature. Hyperkeratotic yellow plaques interspersed with superficial erosions on the torso, scalp, and elbows.
Musculoskeletal: Marked contracture of all extremities with inability to extend beyond 90 degrees. Rounded plantar feet.

LABS/IMAGING

Abnormal:
Chest X-ray: Small clavicles with irregular shape; segments of bone thinning at the lateral ends.
Echocardiogram: PDA, small to moderate left-to-right shunt; mild to moderate TR and bidirectional PFO.
Whole Exome Sequencing: Homozygous variant, c.50delA in ZMPSTE24.

Normal/Negative: DNA microarray, chromosome analysis, Neu-Laxova syndrome test.

DIAGNOSIS

Lethal restrictive dermopathy due to homozygous mutation in ZMPSTE24 gene

TREATMENT AND COURSE

The patient remained ventilator-dependent throughout her hospital course. She did not tolerate enteral feeds despite multiple attempts and remained NPO on parenteral feeds. Skin care was focused on scheduled applications of emollients and infection prevention. After extended discussion on the uniformly-lethal nature of the disorder with her parents, respiratory support was withdrawn, and she died on the 25th day of life.

DISCUSSION

Restrictive dermopathy (RD) is a rare autosomal recessive (AR), lethal disorder, with fewer than 100 cases reported in the literature. RD is classified as a laminopathy. Laminopathies are defined as a group of disorders with mutations of either the LMNA gene or the zinc metalloproteinase gene ZMPSTE24. As a whole, laminopathies result in premature aging syndromes including Hutchinson-Gilford progeria, atypical progeroid syndrome, atypical Werner syndrome and (as in our case) RD.

The product of the ZMPSTE24 gene is a zinc metalloproteinase involved in processing of lamin A. The loss-of-function mutation leads to build up of farnesylated prelamin A (precursor of lamin A), which in turn leads to disruption of the nuclear laminar integrity and defects in nuclear structure and function. RD has a number of distinctive clinical findings, the most characteristic of which is thin, taut, and translucent skin. The non-compliant nature of the skin leads to IUGR, joint contractures, and subsequent decreased fetal movement that in almost all cases lead to PPROM. After birth, patients exhibit an additional number of characteristic physical exam findings including, but not limited to, erosions in flexural regions/sites of pressure (due to taut skin), low set ears, hypertelorism, small pinched nose, micrognathia, "o-shaped" mouth, chemosis, and hypoplastic clavicles. Death usually occurs within days to weeks after birth from restrictive respiratory failure.

While the clinical features of RD are distinctive, the differential diagnosis includes other rare disorders associated with IUGR and abnormal craniofacial features such as Neu-Laxova syndrome (NLS). NLS is a lethal autosomal recessive disorder caused by a mutation in PHGDH gene (involved in serine metabolism). Defects in CNS and skin development lead to clinical features of microcephaly, dysmorphic facial features, proptosis, hypoplasia of skeletal muscles (leading to contractures), syndactyly, edema, and ichthyosis. Other rare syndromes in the differential diagnosis include Pena-Shokeir syndrome and cerebro-oculo-facio-skeletal syndrome. Genetic analysis is often required to distinguish these disorders.

KEY POINTS

1. RD is an AR disorder resulting from a loss-of-function mutation in ZMPSTE24.
2. RD results in IUGR/PPROM with distinctive clinical features that include thin, taut and translucent skin with associated joint contractures, hypoplastic clavicles, and dysmorphic facial features.

REFERENCES

1. McKenna T, et al. Skin Disease in Laminopathy-Associated Premature Aging. J Invest Dermatol. 2015. 135(11):2577-83.
2. Morais P, et al. Restrictive dermopathy--a lethal congenital laminopathy. Case report and review of the literature. Eur J Pediatr. 2009. 168(8):1007-12.
3. Navarro CL, et al. New ZMPSTE24 (FACE1) mutations in patients affected with restrictive dermopathy or related progeroid syndromes and mutation update. Eur J Hum Genet. 2014. 22(8):1002-11.
4. Mok Q, et al. Restrictive dermopathy: a report of three cases. J Med Genet. 1990. 27(5):315-9.
5. Shaheen R, et al. Neu-Laxova syndrome, an inborn error of serine metabolism, is caused by mutations in PHGDH. Am J Hum Genet. 2014. 94(6):898-904.

CHICAGO DERMATOLOGICAL SOCIETY **Case 3**

Presented by Julia Mhlaba, MD and Ahmad Amin, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

UNKNOWN

A 67-year-old male presented with indurated plaques on the left forehead and right dorsal hand

CHICAGO DERMATOLOGICAL SOCIETY **Case 4**

Presented by Jennifer Shastry, MD and Simon Yoo, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 74-year-old Caucasian male with a history of multiple basal cell carcinomas presented for evaluation and treatment of biopsy-confirmed basal cell carcinomas of the right lower extremity.

The patient had a history of basal cell carcinoma of the right leg treated with excision and repaired with a split-thickness skin graft in 2015. In late 2016, the patient noted new lesions on the right lower extremity. Multiple skin biopsies of the right lower extremity were consistent with basal cell carcinoma. He was referred to Northwestern for Mohs micrographic surgery. At the time of presentation, the patient noted a tender, draining lesion on the scrotum and 20 new "blistering" lesions on the right lower extremity. He also reported a longstanding history of scrotal redness, drainage, and pruritus. These symptoms were previously attributed to tinea cruris and treated unsuccessfully with topical antifungals.

PAST MEDICAL HISTORY

Multiple basal cell carcinomas (neck, upper back, right lower extremity) treated with excision, hypertension, gout

MEDICATIONS

Aspirin, allopurinol, lisinopril

PHYSICAL EXAM

Anterior right leg with a 6 cm well-healed skin graft. The scrotum was edematous; on the right lateral aspect, there was a tender red ulcerated plaque. There were numerous shiny erythematous papules and plaques extending from the right inguinal fold to the right anterolateral thigh and the right medial calf. Right lower extremity with diffuse 3+ pitting edema.

LABS/IMAGING

Abnormal:

CT chest/abdomen/pelvis: Two enlarged periportal lymph nodes measuring 1.4 cm and 1.2 cm. Diffuse scrotal wall edema noted; no inguinal mass seen.
CT right lower extremity: Diffuse circumferential soft tissue edema with multifocal areas of cutaneous thickening. A prominent right inguinal lymph node measuring 0.9 x 1.8 cm.

HISTOPATHOLOGY

Dermatopathology consultation of right proximal leg skin biopsy (2015): Basal cell carcinoma, nodular and infiltrating types. Perineural or lymphovascular invasion was not identified.

Dermatopathology consultation of seven right lower extremity skin biopsies (right mons pubis, groin, hip, lateral thigh, anterior thigh, medial thigh, and medial leg; 2017): Basal cell carcinoma, infiltrative and morpheaform types. Intravascular involvement was noted on the right groin biopsy, and the right anterior thigh biopsy demonstrated a focal metatypical process.

DIAGNOSIS

Metastatic basal cell carcinoma

TREATMENT AND COURSE

Due to the size, number, recurrent nature, and location of the patient's basal cell carcinomas, they were deemed inoperable, and the patient was started on vismodegib 150 mg once daily. While the enlarged periportal and inguinal lymph nodes were of unclear significance, regular follow-up imaging was recommended. At a follow-up visit a few days after treatment initiation, the patient was noted to have a new erythematous plaque on his lower back. One month after treatment initiation, the tumors had decreased in size, and his scrotal ulceration had resolved. The patient has since moved to another state, where he has had regular follow-up.

DISCUSSION

While basal cell carcinoma (BCC) is the most common skin cancer in the U.S., with over 2 million individuals affected yearly, metastatic disease is exceedingly rare, with a reported incidence of 0.0028%. The average duration between primary disease and onset of metastasis is 11 years, and the most common sites of metastases are the lymph nodes and lungs, followed by bones and skin. Risk factors for development of metastatic disease include head and neck primary site, prior radiation treatment, morpheaform or metatypical histologic types, perineural invasion, and large primary tumor, with 80% of cases arising from a primary tumor larger than 5 cm.

While the incidence of scrotal BCC is less than 1%, scrotal primary disease is a possibility in our patient given the reported longstanding history of scrotal erythema and symptoms. Literature suggests that metastatic scrotal BCCs may have a shorter interval between onset of primary and metastasis, with an average of 2-3 years, compared to the average of 11 years for all anatomic sites. The prognosis of metastatic BCC is generally poor, with median survival ranging between 8 to 14 months. Until the advent of hedgehog pathway inhibitors, the mainstay of treatment for locally advanced and metastatic BCC was surgical excision and adjuvant radiation therapy.

Alterations in the hedgehog signaling pathway resulting in pathway activation have been demonstrated to drive unrestricted cell proliferation in BCC. Smoothened (SMO) is a transmembrane protein that promotes activation of the hedgehog signaling pathway. Inactivating mutations in Patch1 (PTCH1), a tumor suppressor that inhibits SMO, are present in greater than 90% of BCC tumors. Vismodegib, a small molecule inhibitor of SMO, blocks abnormal activation of the hedgehog signaling pathway and received FDA approval for the treatment of locally advanced or metastatic BCC in 2012.

KEY POINTS

1. While basal cell carcinoma is a common cancer, metastatic disease is rare and presents treatment challenges to the clinician.
2. Primary scrotal basal cell carcinoma may metastasize over a shorter duration than primary disease of other anatomic sites.
3. Vismodegib, an inhibitor of Smoothened, decreases hedgehog signaling pathway activity, which is aberrantly activated in basal cell carcinoma.

REFERENCES

1. Jacobsen A, et al. Hedgehog Pathway Inhibitor Therapy for Locally Advanced and Metastatic Basal Cell Carcinoma: A Systematic Review and Pooled Analysis of Interventional Studies. JAMA Dermatol 2016. 152(7):816-24.
2. Kinoshita R, et al. Basal cell carcinoma of the scrotum with lymph node metastasis: report of a case and review of the literature. Int J Dermatol 2005. 44(1):54-6.
3. Sekulic A, et al. Efficacy and Safety of Vismodegib in Advanced Basal-Cell Carcinoma. N Engl J Med 2012. 366(23):2171-9.
4. Snow SN, et al. Metastatic basal cell carcinoma. Report of five cases. Cancer 1994. 73: 328–35.
5. Tang S, et al. Metastatic basal cell carcinoma: case series and review of the literature. Austral J Dermatol 2016. 58(2):40-3.

CHICAGO DERMATOLOGICAL SOCIETY **Case 5**

Presented by Olivia Schenck, MD[1], Sarah Chamlin, MD[1,2], and Joan Guitart, MD[1]
[1]Department of Dermatology, Feinberg School of Medicine, Northwestern University
[2]Department of Pediatrics & Division of Dermatology, Ann & Robert H. Lurie Children's Hospital of Chicago, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 15-year-old Hispanic female presented for evaluation of a long-standing skin eruption, present since early infancy per her parents' report. She had been seen by other dermatology providers previously and diagnosed with eczema. Treatment with various topical corticosteroids had provided no improvement. Her eruption usually was present in the same locations on her back, arms, abdomen, and legs. Additionally, the patient reported rough skin lesions on her inferior abdomen, bilateral axillae, and thighs, as well as dry, scaly skin in general. She reported occasional "stinging" sensations with the use of certain emollients, but denied any other associated symptoms, including pruritus, bleeding, blistering, or any systemic symptoms. She was referred to the dermatology clinic at Ann & Robert H. Lurie Children's Hospital for further evaluation given her lack of improvement with past therapy.

PAST MEDICAL HISTORY

Asthma, GERD

FAMILY AND SOCIAL HISTORY

No family history of skin cancer, other malignancies, rashes, atopic dermatitis, atopy, or skin problems similar to those of the patient. Denied tobacco or alcohol use.

MEDICATIONS

Albuterol inhaler, fluticasone nasal spray, omeprazole

PHYSICAL EXAM

Erythematous to violaceous patches involving the right back, chest, and extending down the right arm with rough follicular plugging. Similar patches on the left arm, bilateral thighs, mons pubis, popliteal fossae, calves, and ankles with mild lichenification. Atrophic plaques and striae on the right upper back. Right medial thigh with extensive, prominent, wide red striae and one focal dermal nodule. Bilateral thighs with atrophic plaques and prominent telangiectasia. Numerous, diffuse, tan-brown follicularly-based keratotic papules on the inferior abdomen and bilateral axillae, with associated alopecia. Normal capillary loops on finger proximal nail folds. Normal oral mucosa, teeth, scalp hair and nails. Head and neck without lesions. In total, the affected body surface area (BSA) was estimated at 30%. No palpable cervical, axillary, or inguinal lymphadenopathy. No palpable hepatosplenomegaly.

LABS/IMAGING

Abnormal: None

Normal/Negative: CBC with differential, CMP and LDH. Sézary cell count showed rare convoluted lymphocytes, 68/uL absolute number and 2.7% of total lymphocytes (range: 0-250/uL or <5%). Flow cytometric analysis of peripheral blood revealed a heterogeneous T-cell population (CD3+, CD5+, CD7+) without overt phenotypic abnormality and polytypic B cells (CD19+) with no evidence of phenotypic abnormality or clonality. Molecular analysis of peripheral blood was negative for clonal T-cell receptor gene rearrangement.

HISTOPATHOLOGY

Biopsy of a representative area showed mild spongiosis and lymphocytic infiltrate along the dermal epidermal junction and focal exocytosis. Follicular units infiltrated by numerous small to intermediate lymphocytes without mucinous degeneration of the epithelium, but with cystic changes. Adjacent dermis shows an interstitial infiltrate of small lymphocytes extending into the deep dermis with associated fibroplasia and rare histiocytes. Immunohistochemistry showed atypical cells positive for CD2, CD3, CD5, and negative for TIA-1, TCR gamma M1. The CD4:CD8 ratio of the T-cell infiltrate was approximately 10:1. CD7 was expressed in more than 50% of the mononuclear infiltrate.

DIAGNOSIS

Folliculotropic mycosis fungoides

TREATMENT AND COURSE

The patient was started on narrow band ultraviolet B (nbUVB) light therapy two to three times weekly and hydrocortisone 2.5% cream to the affected areas daily. A more potent topical corticosteroid was avoided given the patient's prior use and signs of steroid atrophy. She had mild improvement in her disease at 3-month follow-up.

DISCUSSION

Folliculotropic mycosis fungoides (FMF) is a common variant of mycosis fungoides (MF) representing approximately 4-5% of all cutaneous T-cell lymphomas. As its name implies, FMF is characterized by deep, follicular, and perifollicular localization of atypical lymphocytic infiltrates (typically CD3+, CD4+, CD8- cells), with or without follicular mucinosis. This folliculotropism instead of epidermotropism distinguishes FMF from classic MF. In addition to being a variant of MF, FMF has been proposed to exist along a clinicopathologic continuum with idiopathic follicular mucinosis (IFM). Significant overlap exists between the clinical and pathologic presentations, prognosis, and clinical course of IFM and indolent FMF, particularly in pediatric cases, thereby making it difficult to distinguish them as separate entities. Given her extensive involvement, yet lack of follicular destruction and mucinous degeneration, our patient likely represents a low-grade variant of FMF along this spectrum with IFM.

Clinically, FMF and IFM can present with grouped follicle-based papules, patches, plaques, acneiform lesions, and tumors, with associated alopecia. Given her age, our patient most likely has alopecia associated with the follicular papules in her axilla. In children and adolescents, the most common presentation of FMF consists of asymptomatic hypopigmented patches with follicular accentuation on the trunk and extremities, with sparser perifollicular atypical lymphocytic infiltrates, as in the case of our patient. In contrast, in adults, FMF lesions predominantly involve the head and neck and are often associated with severe pruritus and secondary bacterial infection. With its nonspecific presentation and frequent concomitant presentation with other MF variants, FMF can often mimic benign inflammatory skin diseases, such as atopic dermatitis, psoriasis, keratosis pilaris, and lichen spinulosus.

The ISCL/EORTC* 2007 revised staging system for classic MF is also used for FMF and is based on tumor-node-metastasis-blood (TNMB) stages. The presence of involved BSA >10%, tumoral disease, erythroderma, lymph node involvement, visceral organ involvement, or blood clonal Sézary cell >1000/uL at the time of presentation indicates a higher stage of disease. Interestingly, in a study of juvenile FMF, most cases were characterized by early-stage superficial lesions and a more indolent disease course. Our patient presented with stage IB disease (T2bN0M0B0a stage) given her 30% BSA involvement of largely patches, plaques, and papules and lack of lymph node, organ, or blood involvement.

Distinguishing FMF from classic MF is important due to its traditional association with a poorer prognosis, with 5-year survival rates of 60-70%. However, recent studies have identified a difference in prognosis between early-stage FMF (characterized by patches, plaques, and/or follicular papules with sparse peri-follicular infiltrates) as compared to advanced-stage FMF (more extensive infiltrates with medium- to large-sized tumor cells). The 5-year overall survival and disease-free survival were 92% and 95%, respectively, for early-stage FMF (comparable to early-stage classic MF) as compared to 50% and 59%, respectively, for more advanced-stage FMF. Additionally, a study of pediatric (<22 years old at time of diagnosis) IFM cases revealed largely benign clinical courses, regardless of association with concomitant MF at the time of diagnosis.

Given its traditional designation as a more aggressive disease, FMF was previously treated with more intensive therapies, similar to those used for tumor-stage MF. However, recent studies have shown that indolent, early-stage FMF may be treated with standard skin-directed therapies used for early-stage classic MF. These therapies include potent topical corticosteroids, nbUVB, psoralen plus ultraviolet A (PUVA), and in the case of solitary lesions, local low-dose radiotherapy. Juvenile cases of FMF have been shown to respond well to skin-directed therapies, particularly PUVA, perhaps due to the milder nature of their presentation. Also, due to its overlap with IFM, conservative treatment is particularly advocated for juvenile, indolent FMF cases. In the case of advanced-stage FMF, more aggressive therapies should be considered, including PUVA monotherapy or combination therapy (with local radiotherapy, interferon-alpha, or systemic retinoids), total skin electron beam irradiation, or systemic chemotherapy (for cases of extracutaneous FMF).

* International Society for Cutaneous Lymphomas (ISCL), European Organization of Research and Treatment of Cancer (EORTC)

KEY POINTS

1. FMF should be considered in the differential diagnosis of chronic nonspecific dermatitis with follicular accentuation, particularly in treatment refractory cases.
2. Juvenile FMF differs from adult FMF in its milder presentation with early-stage disease, increased overlap with idiopathic follicular mucinosis, and responsiveness to conservative treatment with topical corticosteroids or phototherapy.
3. The treatment course and prognosis for a patient with FMF can be guided by disease staging and determination between indolent early-stage versus aggressive advanced-stage disease.

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CHICAGO DERMATOLOGICAL SOCIETY **Case 6**

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

UNKNOWN

A female born at 37 weeks gestational age presented at birth with generalized erosions and atrophic plaques

CHICAGO DERMATOLOGICAL SOCIETY **Case 7**

Presented by Joshua L. Owen, MD, PhD and Bethanee J. Schlosser, MD, PhD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 66-year-old African-American male presented with a left periocular wound and swelling. Patient had a history of left-sided trigeminal nerve V1 (ophthalmic) distribution herpes zoster with positive Hutchinson sign that was complicated by herpetic uveitis about 3 years prior. Since that time, he has had significant post-herpetic neuralgia with ongoing dysesthesia and pruritus in the affected area. History was also notable for a recent excisional biopsy of an enlarged left cervical lymph node.

PAST MEDICAL HISTORY

Herpes zoster (left V1 distribution), herpes uveitis (OS), enlarged left cervical lymph node

MEDICATIONS

Gabapentin, hydroxyzine, trazodone

PHYSICAL EXAM

Involving the patient's face and scalp, there was a sharply demarcated, irregular, approximately 6 cm by 20 cm ulcer to a depth of the superficial fascia extending from the left supraorbital rim across the frontal and parietal scalp, stopping abruptly anterior to the occipital scalp. There was also significant ipsilateral edema and erythema periorbitally without involvement of the eye itself.

LABS/IMAGING

Abnormal: WBC 12.5 (ref: 3.5-10.5 K/UL), absolute PMNs 10.2 (ref: 1.5-8.0 K/UL), Hgb 11.1 (ref: 13.0-17.5 g/dL)

Normal/Negative: CMP, platelet count

HISTOPATHOLOGY

Left cervical lymph node biopsy: Follicular hyperplasia and polytypic plasmacytosis. Flow cytometric analysis demonstrated T cells and B cells with an unremarkable immunophenotype.

DIAGNOSIS

Extensive trigeminal trophic syndrome, resulting in preseptal cellulitis

TREATMENT AND COURSE

Ophthalmology was consulted and ruled out orbital cellulitis. The patient was initially treated with intravenous clindamycin and transitioned to oral clindamycin upon discharge.

Further anamnesis revealed that the patient experienced ongoing pruritus despite several therapies. He had previously been prescribed amitriptyline, doxepin, pregabalin, and gabapentin. Plastic surgery had also performed several procedural interventions including trigeminal nerve blocks; neurotomies of the supraorbital, supratrochlear, and auriculotemporal nerves; and free muscle grafts to the involved area. All interventions were unsuccessful in ameliorating the patient's symptoms or providing durable benefit to the wound. The patient freely admitted to scratching or picking at the ulcerated area, noting that he often does not realize he is doing it. We educated him that the area needs to be treated like a chronic, non-healing wound. We provided wound care recommendations, and the patient was asked to follow up as an outpatient to discuss additional medical and additional wound care therapies.

DISCUSSION

Trigeminal trophic syndrome (TTS) is a rare, chronic, ulcerative disease in the distribution of the trigeminal nerve. The first step is injury to at least 1 branch of the trigeminal nerve, either directly or indirectly. The most common cause of direct nerve injury is trigeminal nerve ablation for trigeminal neuralgia. The most common cause of indirect nerve injury is cerebrovascular accident (most commonly Wallenberg's lateral medullary syndrome and vertebrobasilar insufficiency). Other etiologies include craniofacial surgery, trauma, herpes zoster infection, herpes simplex virus infection, intracranial meningioma, and other intracranial neoplasms.

The interval between damage to the trigeminal nerve and ulceration can vary from weeks to decades. During this time period, the second step in the development of TTS is the onset of a persistent dysesthesia, which has been described as itching, tickling, burning, or crawling. Most often there is an associated anesthesia in the affected area. Patients then rub or pick at the area in an attempt to relieve this sensation, leading to ulceration. TTS most commonly involves the V2 (maxillary) branch of the trigeminal nerve, resulting in an ulcer of the nasal ala. The tip of the nose is often spared as it is innervated by the anterior ethmoidal branch of the nasociliary nerve, a distal branch of the V1 (ophthalmic) branch. However, TTS ulcers can involve any of the trigeminal nerve branches, including more than one. Infrequently, extensive ulceration of the scalp, oral cavity, tongue, eyelid, eye, and ulceration through frontal scalp into the brain has been observed.

Depending on the location and extent of ulceration, the differential diagnosis could include infections (bacteria including syphilis, mycobacteria, deep fungal, leishmaniasis), neoplasms (SCC, BCC, lymphoma), granulomatosis with polyangiitis, pyoderma gangrenosum, and factitial dermatitis. An important distinction from factitial dermatitis is that patients with TTS do not have an underlying psychologic or cognitive condition that results in the picking/compulsive skin manipulation; rather the skin manipulation occurs in response to an abnormal cutaneous sensation.

Treatments for TTS ideally address both the dysesthesia as well as the habit of picking. Physical blocking modalities that have been tried with varying success include keeping nails short, wearing gloves at night, bespoke thermoplastic facemask, and application of a wound vac. Pharmacologic treatment of the dysesthesia has included oral gabapentin, carbamazepine, pregabalin, pimozide, and amitriptyline. Review of the literature reveals that the most commonly used medication was gabapentin followed by carbamazepine. Surgical interventions have also been attempted with varying levels of success, including pedicle flaps, free flaps, and thermoplastic dressings.

KEY POINTS

1. Trigeminal trophic syndrome is a disorder of self-induced ulceration in the distribution of the trigeminal nerve, occurring weeks to decades after injury to the nerve.
2. Successful treatment requires early recognition, patient education regarding the self-induced nature, and a multidisciplinary approach that addresses the dysesthesia as well as the habit of picking.

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CHICAGO DERMATOLOGICAL SOCIETY **Case 8**

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

HISTORY OF PRESENT ILLNESS

A healthy 4-year-old male presented with a two-month history of cutaneous plaques on the lower legs and ankles. The lesions first developed as small, non-tender, erythematous plaques that slowly expanded and spread to involve both legs. He was initially diagnosed by another provider with possible subcutaneous granuloma annulare and was treated with a one-month course of topical clobetasol without improvement. Ultrasound imaging was nonspecific and suggested a superficial process. Skin biopsy was performed. His lesions remained asymptomatic, and he was otherwise healthy with a negative review of systems. He was referred to Ann & Robert H. Lurie Children's Hospital of Chicago for further evaluation.

PAST MEDICAL HISTORY

Normal birth and growth milestones

FAMILY HISTORY

Mother with multiple sclerosis

MEDICATIONS

Clobetasol 0.05% ointment

PHYSICAL EXAM

The lower legs and ankles had several 2-4 cm firm, annular, and nodular plaques with central brown to yellow pigmentation, central atrophy, and peripheral erythema.

LABS

Abnormal: ESR 16 s (ref < 15 s), IgE 157 kU/L (ref < 90 kU/L)

Normal/Negative: CBC, CMP, lipid panel, Hgb A1C, TSH/T4, CRP, C3/C4/CH50, IgM/IgG/IgA, ANA, anti-dsDNA Ab, anti-TPO Ab, anti-thyroglobulin Ab, anti-phospholipid Ab, CK, LDH, aldolase, fecal calprotectin, stool guaiac, quantitative G6PD, alpha-1-antitrypsin phenotype

HISTOPATHOLOGY

A deep punch biopsy showed mild perivascular inflammation extending into the deep reticular dermis, deep fibroplasia, and a mixed inflammatory infiltrate within the lobular component of the subcutis composed of histiocytes, plasma cells, and lymphocytes without atypia or rimming. The infiltrate was mostly histiocytic with few B and T cells in normal ratios and with a CD4:CD8 ratio of 4:1 (within normal limits). Special stains for microorganisms were negative. A non-specific lobular panniculitis was favored, without features of hemophagocytosis, granulomatous changes, atypia, or a neutrophilic process.

DIAGNOSIS

Lipoatrophic panniculitis

TREATMENT AND COURSE

The patient was treated with two courses of oral prednisone over two months, which resulted in softening of existing lesions and improvement in the degree of erythema and pigmentation, without the development of new lesions. He was then started on oral methotrexate (MTX) at an

initial dose of 0.1 mg/kg/week then titrated up to 0.3 mg/kg/week, along with daily folic acid supplementation. Follow-up at seven months showed mild progression of disease in the form of new lipoatrophic plaques on the buttocks, shins, and ankles without overt clinical inflammation. The patient completed an additional oral prednisone course tapered over one month and has continued weekly MTX without further flares to date. He continues to remain otherwise well with normal activity level, no fevers, normal exercise tolerance, and no reported pain.

DISCUSSION

Lipoatrophy, a selective loss of subcutaneous adipose tissue, can present in a localized, partial, or generalized fashion. Localized lipoatrophy most commonly occurs in the setting of certain medications, trauma, surgery, or as a result of panniculitis. Lipoatrophic panniculitis is a poorly understood, localized lipoatrophy occurring mainly in children. This rare condition has been described by many names including lipophagic panniculitis, connective tissue panniculitis, annular lipoatrophic panniculitis of childhood, and annular atrophy of the ankles. Although no associated diseases are identified in many patients, the condition may occur in association with diabetes mellitus, systemic lupus erythematosus, juvenile dermatomyositis, juvenile idiopathic arthritis or hypothyroidism.

Lipoatrophic panniculitis initially presents as radially enlarging, erythematous plaques and nodules of the extremities, variably accompanied by preceding viral infection, fever, malaise, myalgias, arthralgias, and/or elevated acute phase reactants. The acute inflammatory phase is self-limited and usually restricted to the subcutaneous fat, though involvement of the joints and long bones has been reported. The chronic phase is characterized by circumferential lipoatrophy of the affected extremities. The initial clinical presentation has a broad differential diagnosis (e.g., granuloma annulare, erythema nodosum, lupus profundus, subcutaneous panniculitis-like T cell lymphoma), however, histopathologic analysis shows a unique combination of lobular panniculitis (without vasculitis), atrophy of the fat lobule with compensatory fibrosis, and an inflammatory infiltrate initially composed of neutrophils and lymphocytes that are eventually replaced with lipid-laden histiocytes.

There is no treatment consensus. Reported therapies include systemic corticosteroids, MTX, anti-malarial agents, dapsone, cyclosporine, and biologic agents such as etanercept. Though the etiology of lipoatrophic panniculitis is currently unknown, current hypotheses suggest an association with underlying autoimmune disease or autoinflammation (e.g., proteasome–associated autoinflammatory syndromes such as CANDLE syndrome). Lipoatrophic panniculitis is a diagnosis of exclusion and requires a thorough serologic and histopathologic evaluation for other panniculitides, vasculitis, foreign-body reactions, infection (including fungal and mycobacterial), immunodeficiency (both intrinsic and acquired), and autoimmune conditions.

KEY POINTS

1. Lipoatrophic panniculitis is a rare cause of localized lipoatrophy in children.
2. Lipoatrophic panniculitis, has a broad clinical differential, however histopathology shows a distinctive pattern of lobar panniculitis, fat atrophy, and lipophage accumulation.
3. There are no established treatment guidelines for lipoatrophic panniculitis, but immunosuppressive, cytotoxic, anti-malarial, and biologic agents have all shown benefit.

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CHICAGO DERMATOLOGICAL SOCIETY **Case 9**

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

UNKNOWN

A 62-year-old Nigerian female presented with a twenty-year history of violaceous papules and plaques on the lower extremities

CHICAGO DERMATOLOGICAL SOCIETY **Case 10**

Presented by Amin Esfahani, MD, MSc and Lauren Guggina, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 67-year-old male was admitted to the hospital for severe sepsis with new-onset pancytopenia. The patient was on day 19 status-post simultaneous liver-kidney transplantation (SLKT) for hepatocellular carcinoma (HCC). On admission, he was found to have a *Klebsiella pneumoniae* (ESBL positive) and *Enterococcus faecium* urinary tract infection. On day 4 of his hospitalization, he developed diarrhea and a new cutaneous eruption. Dermatology was consulted for further evaluation.

PAST MEDICAL HISTORY

Chronic kidney disease s/p SLKT, type 2 diabetes mellitus, HBV cirrhosis complicated by HCC s/p SLKT, hyperlipidemia, hypertension

SOCIAL HISTORY

Born in Mexico; history of heavy alcohol use in 1990s, but quit in 2003

MEDICATIONS

Antimicrobials: Amikacin, daptomycin, meropenem, atovaquone, entecavir, valganciclovir
Immunosuppressive: Prednisone, tacrolimus
Other: Pantoprazole, tbo-filgrastim, heparin, calcium-vitamin D, magnesium oxide, thiamine, aspirin, insulin glargine, simvastatin, tamsulosin

PHYSICAL EXAM

The examination of the abdomen revealed healing surgical scars. Also present was ill-defined erythema with interspersed partially blanching macules and papules. Extending from the posterior neck to posterior thighs was diffuse reticular, violaceous, partially blanching macules and patches with faint erythema on the lateral edges.

LABS/IMAGING

Abnormal:

Labs: WBC 1.8 (ref 3.5-10.5 K/UL), RBC 3.1 (ref 4.3-5.8 M/UL), Hgb 8.8 (ref 13.0-17.5 g/dL), Hct 25.6 (ref 38.0-55.0%), platelet count 115 (ref 140-390 K/UL), LDH 426 (ref 0-271 U/L), bicarbonate 18 (ref 21-31 mEq/L), calcium 7.7 (ref 8.3-10.5 mg/dL), albumin 2.6 (ref 3.5-5.7 g/dL), BUN 38 (ref 2-25 mg/dL); glucose 405 (ref 65-100 mg/dL), protein 4.7 (ref 6.4-8.9 g/dL), T bili 1.3 (ref 0.0-1.0 mg/dL).

CT Chest/Abdomen/Pelvis: No focus of infection identified; new ascites
Liver ultrasound: New ascites; possible hepatic artery stenosis

Normal/Negative:

Labs: Sodium, potassium, chloride, creatinine, ALT, AST, Alk Phos, D bili, DIC panel, lactic acid, blood cultures, *C. difficile* PCR, stool Norovirus antigen, CMV
Urine culture: No growth (at admission: *Klebsiella pneumoniae* ESBL+ and *Enterococcus faecium)*

HISTOPATHOLOGY

Biopsy of the right hip revealed a mild interface lymphocytic infiltrate without significant vacuolar changes of the basal cells. The epidermis showed focal hyperkeratosis and necrotic cells.

PRELIMINARY DIAGNOSIS

Suggestive of acute graft-versus-host disease (GVHD)

TREATMENT AND COURSE

Simultaneous work-up was performed to determine the etiology of diarrhea and pancytopenia. No infectious causes were identified. Two biopsies from the colon showed crypt necrosis and apoptosis suggestive of GVHD (staining for CMV negative). A bone marrow biopsy demonstrated marked hypocellularity consistent with bone marrow failure. Confirmatory testing showed evidence of macrochimerism with the presence of 18% and 25% donor cells in the peripheral blood and bone marrow, respectively. A diagnosis of acute GVHD was made. Treatment was initiated by increasing the dose of the patient's immunosuppressive medications (corticosteroids and calcineurin inhibitors). Given the extent of bone marrow involvement, treatment with rabbit anti-thymocyte globulin (ATG) was initiated with the plan to bridge to a bone marrow transplant. However, the patient's cardiopulmonary status and pancytopenia continued to worsen, and he died on day 38 post-SLKT from septic shock secondary to *Klebsiella pneumoniae*.

DISCUSSION

GVHD is a rare complication of solid organ transplant (SOT). The incidence is organ-dependent with the highest reported rates occurring in small bowel transplant recipients (<5%) followed by liver transplant recipients (0.5-2%). In contrast, the incidence of GVHD in hematopoietic stem cell transplant (HSCT) has been reported in the literature to be as high as 50%. The pathophysiology of GVHD has been hypothesized to revolve around a three-phase process that leads to an exaggerated immune response from the host and donor immune systems. In the first phase, the damage to the host tissue (from underlying disease, infections, and conditioning regimens) coupled with exposure of donor tissue to a foreign environment leads to a pro-inflammatory environment and activation of antigen presenting cells (APCs). In the second phase, the APCs activate donor naïve T-cells, and in the final phase, these activated donor T-cells mediate tissue damage. Even though a liver graft can contain as many lymphocytes as HSCT, it is still not fully understood why the rates of GVHD are significantly lower following SOT compared to HSCT. Some have hypothesized that this may be due in part to relatively lower levels of iatrogenic immunosuppression in SOT recipients leading to a better ability to eradicate donor T cells.

The current understanding of the presentation, course, and prognosis of GVHD in SOT comes from case reports and few case series (most with fewer than ten cases each). The majority of the current literature is derived from liver transplant patients, with approximately 200 reported cases. Currently, the median time from transplant to development of GVHD is estimated to be 25-40 days. A nonspecific skin eruption is the most common and often the earliest clinical feature (60-95%). This is followed by involvement of the GI system (60-65%) often presenting as diarrhea and in severe cases as a GI bleed. Bone marrow involvement, presenting as cytopenia is also very common (55-78%), especially in the liver transplant population. Furthermore, approximately 50% of patients develop fever, which is thought to be secondary to the systemic pro-inflammatory immune response. It is worth noting that the liver function abnormalities are often absent. This is contrast to HSCT-related GVHD, where liver function abnormalities are common and used as part of the grading system. The median time from presentation to diagnosis of GVHD is approximately 14 days, and this delay in diagnosis has been attributed to the previously discussed nonspecific symptoms (cutaneous eruption, diarrhea, cytopenia, and fever), which can alternatively be attributed to infection or medication. The best diagnostic tools include sampling of the involved organs such as biopsies of skin, colon, or bone marrow. Two common confirmatory tests include fluorescence in-situ hybridization (FISH) for X-Y chromosome (if there is a sex-mismatch between the donor and recipient) and short tandem repeat PCR for evaluation of macrochimerism (defined as >1% donor cells) in affected organs.

There is currently no standardized treatment algorithm for the management of GVHD in SOT. Treatment regimens are based on experience with GVHD in HSCT. First-line therapy includes increased immunosuppression with oral corticosteroids and calcineurin inhibitors. Second-line therapies include TNF-α inhibitors, IL-2 antagonists (e.g. basiliximab or daclizumab), CD2 inhibitors (alefacept), ATG, and extracorporeal photopheresis. In contrast, some case reports have shown improved clinical outcomes with a decrease in patient's immunosuppression to allow for a better host response. However, a recent comprehensive review did not find a statistically significant difference in mortality between decreasing or increasing immunosuppressive regimens in patients with SOT associated GVHD. Overall, treatment is extremely challenging, as the degree of immunosuppression must be weighed against the risk of death from sepsis. This is especially critical in patients with bone marrow failure. The mortality from GVHD in liver transplant recipients is approximately 80% within 6 months of diagnosis; often from sepsis or GI bleed secondary to bone marrow invasion. The mortality from GVHD in any other SOT appears to be similar. Children have a better prognosis with mortality rates reported around 30%.

KEY POINTS

1. GVHD is a rare, but highly fatal complication of SOT.
2. A nonspecific cutaneous eruption is usually the first and most common manifestation of SOT GVHD.

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Please use the following link for access to information regarding on-going Dermatology clinical trials at Northwestern University:

http://www.feinberg.northwestern.edu/sites/dermatology/research/clinical-trials.html