Chicago Dermatological Society

December 2013
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Saturday, December 14, 2013

Conference Host:
Section of Dermatology
University of Chicago Hospitals
Chicago, Illinois

Program

Conference Location

University of Chicago
Duchossois Center for Advanced Medicine (DCAM)
5758 S. Maryland Ave.

8:30 a.m.	**Registration Opens** *DCAM Main Lobby (near the elevators)* Continental Breakfast Exhibitors (open throughout conference) *4th Floor South Atrium*
9:00 a.m. - 10:00 a.m.	**Resident Lecture** – *4th Floor North Atrium* "Unwanted Hair Growth" *Robert Dellavalle, MD, PhD, MSPH*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** Patient & Poster Viewing *Dermatology Clinic 3A (DCAM - 3rd floor)* Slide Viewing *DCAM 1st Floor, Suite D, Room 1333*
11:00 a.m. - 12:00 p.m.	**General Session** - *4th Floor North Atrium* LORINCZ LECTURE: "My Adventures in Skin Cancer Prevention" *Robert Dellavalle, MD, PhD, MSPH*
12:00 p.m. - 12:30 p.m.	**Box Lunches & visit with exhibitors** *4th Floor South Atrium*
12:30 p.m. - 12:45 p.m.	**CDS Business Meeting** – *4th Floor North Atrium*
12:45 p.m. - 2:30 p.m.	**Case Discussions** – *4th Floor North Atrium*
2:30 p.m.	**Meeting adjourns**

Mark the Date!

- CDS Coding Seminar – Wednesday, January 15, 2014; Stephens Convention Center, Rosemont
- President's Conference & Awards Luncheon – Wednesday, February 26, 2014; Stephens Convention Center, Rosemont

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

Guest Speaker

ROBERT DELLAVALLE, MD, PHD, MSPH

Chief, Dermatology Service, V.A. Medical Center; Associate Professor of Dermatology; University of Colorado School of Medicine
Denver, Colorado

Delivering the Allan Lorincz Lecture

In addition to serving as an Associate Professor of Dermatology at the University of Colorado School of Medicine, Dr. Dellavalle is Associate Professor of Epidemiology at the Colorado School of Public Health. He has a Chicago connection having earned his medical degree at the University of Chicago (1996) and a PhD in Molecular Genetics & Cell Biology (1993). Dr. Dellavalle completed his dermatology residency at the University of Colorado (2001). He is Dermatology Section Editor for UpToDate, Web and Facebook page Editor for the Journal of the American Academy of Dermatology, Assistant Evidence-Based Dermatology Section Editor for the Archives of Dermatology, and Chair of the VA Dermatology Field Advisory Committee. His academic and clinical interests include clinical research, skin cancer treatment and prevention, public health, evidence-based medicine, residency training, and adult aesthetic dermatology. He has numerous professional activities and publications to his credit.

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Meeting Series"

December 14, 2013 *Chicago, IL*

OBTAINING YOUR CERTIFICATE OF CREDIT

Participants must attend the entire session to receive credit. Please sign the CME attendance sheet at the CDS registration table before you leave the conference. Also, we ask that you complete the evaluation form and return it to us. A certificate will be sent by regular mail to you upon conclusion of the meeting. The information collected as part of this process represents an important part of the CME planning process. CFMC will retain a record of attendance on file for six years.

JOINT SPONSORSHIP STATEMENT

This educational activity is jointly sponsored by CFMC and the Chicago Dermatological Society.

GOAL / PURPOSE

To broaden the clinical knowledge of dermatologists.

TARGET AUDIENCE

This activity has been designed to meet the educational needs of physicians and other healthcare professionals.

FACULTY

Robert Dellavalle, MD, PhD, MSPH

EDUCATIONAL OBJECTIVES

Upon completion of 2013/2014 series of conferences, participants should be able to:

1. Discuss key factors in the diagnosis and treatment for a variety of dermatologic diseases and conditions, including psoriasis, hair disorders, and dermatological symptoms of systemic diseases.

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

PHYSICIAN ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of CFMC and the Chicago Ophthalmological Society. CFMC is accredited by the ACCME to provide continuing medical education for physicians.

CFMC designates this live activity for a maximum of 4.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

OTHER HEALTHCARE PROFESSIONALS STATEMENT

This educational activity has been planned and implemented following the administrative and educational design criteria required for certification of health care professions continuing education credits. Registrants attending this activity may submit their certificate along with a copy of the course content to their professional organizations or state licensing agencies for recognition for 4.5 hours.

DISCLOSURE STATEMENT

It is the policy of CFMC and the Chicago Dermatological Society that the faculty discloses real or apparent conflicts of interest relating to the topics of the educational activity.

Robert Dellavalle, MD, PhD, MSPH: Consultant – World Health Organization

All other members of the faculty and planning team have nothing to disclose nor do they have any vested interests or affiliations.

TABLE OF CONTENTS

PRESENTERS

Adena E. Rosenblatt MD, PhD, and Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS

An otherwise healthy 58-year-old Caucasian male presented to dermatology with multiple nodules mostly localized to his scalp but also on his trunk and extremities. He noticed the first lesion over 30 years ago and the nodules have been increasing in number and in size since that time. The patient denies any pruritus or pain of the nodules. The patient reports that his paternal grandmother, father, and sister have similar lesions.

PAST MEDICAL HISTORY

Patient has a history of seasonal allergies but no other significant medical problems other than listed above.

FAMILY HISTORY

Paternal grandmother, father, and sister with similar cutaneous lesions

MEDICATIONS

Zyrtec PRN

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

58-year-old Caucasian male with multiple soft pink smooth nodules with arborizing blood vessels ranging from 5mm to 3cm. The largest nodule located on the vertex of the scalp had a central superficial erosion with overlying hemorrhagic crust. He also has a few similar lesions on his trunk, groin, and extremities.

DERMATOPATHOLOGY

Proliferation of basaloid cells with little cytoplasm found in interlocking jigsaw puzzle-like nests in the dermis. Islands are outlined by deeply eosinophilic basement membrane with some deeply eosinophilic hyaline droplets within the islands. There is no involvement of the epidermis.

LABORATORY DATA

None

DIAGNOSIS

Multiple cylindromatosis

TREATMENT AND COURSE

The patient has since undergone excision of 10 cylindromas by plastic surgery and is doing well.

DISCUSSION

A cylindroma is a benign undifferentiated adnexal tumor of apocrine and eccrine lineage commonly found on the head and neck, particularly the scalp. They can also be found on the trunk and genitalia. Rarely, these lesions can develop into malignant cylindromas (1). These tumors are thought to arise from pluripotent stem cells in the hair follicle. The size of the tumors can vary from 0.5-6 cm. The tumors can coalesce and form a confluent mass, historically termed “turban tumors.” Cylindromas occur more frequently in women and usually arise it the third decade of life. The tumors typically are pink and firm with

arborizing blood vessels on the surface and a yellowish, homogenous appearance when bisected.

Multiple cylindromatosis is an autosomal dominant condition associated with a mutation in the CYLD gene on chromosome 16q (2). The CYLD encodes a deubiquinating enzyme that impedes the nuclear factor (NF-kB) and c-Jun N-terminal kinase (JNK) pathways (3). However, the exact mechanism of tumorogenesis has not been fully elucidated. Multiple cylindromatosis, Brooke-Spiegler syndrome, and multiple familial trichoepithelioma syndrome were originally thought to be distinct entities. However, currently these conditions are thought to be phenotypic variants of the same underlying CYLD gene mutation (4). Brooke-Spiegler syndrome is characterized by the development of multiple cylindromas as well as trichoepitheliomas and spiradenomas. Multiple familial trichoepithelioma syndrome presents with just trichoepitheliomas. There is an increased risk of secondary basal cell carcinoma in patients with trichoepithelomas.

The definitive treatment for cylindromas is surgical excision and recurrence is uncommon after complete excision. Other treatment options have been tried for patients with multiple cylindromatosis including laser (ie CO2, Nd:Yag, Erb:YAG) and electrosurgery (5).

REFERENCES

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PRESENTERS

Adaobi I. Nwaneshiudu, MD, PhD, Arlene Ruiz de Luzuriaga MD, MPH, Sheryl Hoyer, MD

HISTORY OF PRESENT ILLNESS

An 85 year-old white female, with history of muscle-invasive transitional cell (urothelial) cancer status post transurethral resection of bladder tumor (TURBT) and chemotherapy, presented with a 2-month history of red bumps on her legs. She was treated with cephalexin for presumed cellulitis, and subsequently with ciprofloxacin for presumed "bathtub folliculitis," with no improvement. The lesions were initially asymptomatic but became painful and increased in number over time. She also had persistent leg swelling and was diagnosed with a deep vein thrombosis of the right lower extremity, during a recent hospitalization for a fall due to orthostatic hypotension, and gross hematuria. At that time, the lesions were noted and treated as a cellulitis with clindamycin and ceftriaxone.

PAST MEDICAL HISTORY

Urothelial bladder cancer (stage IV), initially diagnosed in August 2006; deep vein thrombosis in her right lower extremity s/p IVC filter; coronary artery disease, hyperlipidemia, hypertension, gastroesophageal disease, osteoporosis, depression, iron deficiency anemia, carotid stenosis, bradycardia s/p pacemaker

FAMILY HISTORY

Family history: sister with pancreatic cancer, father with coronary artery disease

MEDICATIONS

Levothyroxine, lisinopril, omeprazole, venlafaxine, tolterondine, calcium carbonate/vitamin D3, ferrous sulfate, warfarin

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

There were multiple, erythematous, infiltrative, tender nodules, and erythematous plaques on bilateral lower extremities, worse on the thighs. A solitary erythematous plaque on left mid abdomen was noted. The right lower leg had 3+ pitting edema.

DERMATOPATHOLOGY

On histopathology, there were sheets and cords of cohesive, atypical epithelioid cells with eosinophilic cytoplasm and nuclear pleomorphism, similar to her known primary urothelial carcinoma. Immunohistochemistry revealed CK7 and CK20 positivity in the neoplastic cells.

LABORATORY DATA

None

IMAGING STUDIES

Computer tomography (CT) scan of abdomen and pelvis revealed left hydronephrosis/hydroureter due to obstruction at ureterovesicular junction from a nodular bladder wall mass. There was extensive pelvic and retroperitoneal lymphadenopathy as well as a lesion noted in the liver.

DIAGNOSIS

Cutaneous metastasis of urothelial (transitional cell) bladder cancer

TREATMENT AND COURSE

The patient followed up with hematology/oncology, and the decision was made to undergo palliative management. The patient is being treated with a PD1/L1 inhibitor trial drug, with continued progression of disease. Painful ulceration of the skin lesions have developed. The patient is currently home-bound, living with her daughter, and the ulcers are managed with Vaseline and non-adherent dressing. Topical lidocaine is also being used for pain control of the skin lesions.

DISCUSSION

Cutaneous metastasis from primary visceral malignancies is an uncommon manifestation of advanced disease. The most common primary tumor metastasizing to the skin is breast cancer in women and lung cancer in men. Four basic mechanisms of metastatic spread to skin have been described and include direct invasion from the underlying neoplasm, implantation from surgery, lymphatics, and hematogenous spread.[1]

The most common sites of metastatic disease from urologic malignancies include regional nodes, liver, lung, and bone. The incidence of cutaneous metastasis from urologic malignancies is approximately 1.3%.[1] Clinical appearance of cutaneous metastasis of genitourinary malignancies are typically of three types; nodular (majority), inflammatory, and cicatricial/sclerodermoid.[1] Abdominal skin appears to be the most common metastatic skin site for all genitourinary malignancies.

Bladder cancer is the 4th most common cancer in men and 9th most common in women in the United States.[3] Transitional cell (urothelial) carcinoma is the most common bladder cancer (90% of cases), followed by squamous cell carcinoma (7%) and adenocarcinoma (2%).[2] Metastasis from transitional cell carcinomas is related to depth of penetration of bladder wall, tumor grade and tumor size, with depth of muscle penetration being the single most important factor in prognosis. Cutaneous metastasis is exceptionally rare from all primary bladder malignancies, with a reported incidence of 0.84%.[1] The most common presentations of metastatic bladder cancer are infiltrated plaques or nodules, but may mimic common skin disorders, including erysipelas- or cellulitis-like inflammatory lesions,[2] zosteriform inflammatory lesions, "frog spawn" lymphatic malformation,[5] and subcutaneous nodules.[6]

On histopathology, neoplastic cells predominantly involve the dermis, with a grenz zone, and extension into subcutis. There is disordered proliferation of atypical cells infiltrating in nests and cords, dissecting through collagen bundles of the dermis with minimal epidermal involvement. Individual cells showed abundant cytoplasm, hyperchromatic atypical nuclei and frequent mitosis. The presence of lymphovascular invasion further heightens suspicion for metastasis. Cutaneous metastases usually demonstrate the histologic characteristics of the primary lesion but may be poorly differentiated or anaplastic. Immunohistochemistry is important in the diagnosis of cutaneous metastasis. Neoplastic cells in transitional cell carcinoma are CK7/20 positive. The differential diagnosis of this staining pattern includes pancreatic carcinoma, cholangiocarcinoma, and rarely gastric carcinomas.

Cutaneous metastases from transitional cell carcinoma are rare and are frequently associated with deeply invasive tumors into or beyond the muscularis propria of the bladder. The majority present clinically as locoregional skin disease involving the abdomen, thigh and genitalia due to lymphatic spread or iatrogenic seeding but rarely have distant skin mets.[4] Laboratory analysis typically reveals elevated CA 19-9 and CEA.[4] The median survival is dismal with an average of 6 months from presentation of cutaneous metastasis. Early diagnosis of cutaneous metastasis of bladder cancer may increase survival due to early treatment, with median survival time of 13-24 months.[1]

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PRESENTERS
Monique Kamaria, MD, Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
A full term infant born via cesarean section to nonconsangiuneous parents was noted to have a collodion membrane with prominent ectropion upon delivery. Her APGAR scores were 9 and 9. She was transferred to our neonatal intensive care unit for further care on day of life six. Ophthalmology, genetics, endocrine and neurology also evaluated the newborn upon transfer.

PAST MEDICAL HISTORY
There were no complications throughout the pregnancy. Newborn screen showed possible congenital hypothyroidism.

FAMILY HISTORY
Eczema

MEDICATIONS
Acetaminophen, erythromycin ophthalmic ointment, Aquaphor, morphine, nystatin oral suspension, mupirocin ointment

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Vitals were unremarkable. Infant was alert and active, with a normal suck reflex. A shiny taut membrane, without underlying erythema, encased the newborn. Eclabium and ectropion were noted on exam. Taut fingers and toes were also visible. Prominent linear cracks and separation of the membrane in intertriginous areas were identified. On neurologic exam, mild hyperreflexia and decreased mobility of the lower extremities was noted.

DERMATOPATHOLOGY
A punch biopsy from the thigh preformed at the outside hospital demonstrated compact orthokeratosis, keratotic follicular plugging, and hypogranulosis consistent with congenital ichthyosis.

LABORATORY DATA
Complete blood count: Leukocytes 10.1 K/μL (3.5-17.7), hemoglobin 12.9 g/dL (9.8-17.6), platelets 252 K/μL (150-450)
Differential: Neutrophils 33%, lymphocytes 42%, monocytes 15%, eosinophils 7%, bands 2%
Basic metabolic panel: Glucose 109 mg/dL (60-109), sodium 142 mEq/L (134-149), potassium 4.4 mEq/L (3.5-5.0), chloride 108 mEq/L (95-108), carbon dioxide 23 mEq/L (23-30), BUN 2 mg/dL (7-20), creatinine 0.7 mg/dL (0.5-1.4), calcium 9.3 mg/dL (8.4-10.2)
Free T4 (thyroxine): 1.84 ng/dL (0.9-1.7)
Triiodothyronine: 139 ng/dL (80-195)
Thyrotropin (TSH): 14.67 mcU/mL (0.30-4.00)
Blood cultures: negative

DIAGNOSIS
Neonatal collodion membrane evolving with bathing suit ichthyosis

TREATMENT AND COURSE

Over the hospital course, the membrane continued to shed and desquamate, with improvement in ectropion, eclabium, and tautness of digits. Vaseline was applied to the skin every four hours and lubricating eye drops every 2 hours. Gentle bathing was performed. The infant was initially placed in an isolette with low temperature and high humidity settings until much of the membrane had peeled off and the infant was maintaining her temperature normally. All systemic, topical and ophthalmic antibiotics were discontinued. She remained afebrile throughout and did not have any electrolyte abnormalities. She transitioned from nasogastric to oral feeds without difficulty. Genetic testing was not pursued at this time, and it was recommended that the patient's development be followed closely. The infant was discharged on day of life 12.

Over the course of the next several months, the child developed ichthyosis with plate-like scale limited to the trunk and intertriginous zones. The trunk eventually resolved with post-inflammatory hyperpigmentation, however the axilla and groin were persistently ichthyotic. Frequent use of emollients (Vaseline) every 4 to 6 hours and baking soda baths two times per week were recommended. At eight months, in addition to ichthyosis, the child developed mild atopic dermatitis and her skin regimen was changed to include Cerave cream, Dermasmoothe oil for the scalp, and fluocinolone 0.025% ointment to active areas of rash on the body as needed for flares. She has seen otolaryngology for disimpaction of hyperkeratotic scale from the auditory canals.

Thyroid labs normalized within the first month of life. Further neurologic exams did not reveal persistent abnormalities and the child continues to reach all her developmental milestones.

DISCUSSION

The incidence of babies born with collodion membranes ranges from 1 in 50,000 to 1 in 100,000[1]. Collodion membranes present at birth, with a shiny taut parchment-like membrane stretched over the skin, leading to digital pseudocontractures and distortion of facial features with ectropion and eclabium. The membrane typically sheds spontaneously within the first few weeks of life. Most babies are full term, and a slight male predominance has been observed[2].

It is an evanescent condition of the newborn, and often precedes the development of various genetic ichthyotic disorders, most commonly lamellar ichthyosis and nonbullous congenital ichthyosiform erythroderma. Other associated syndromes include but are not limited to bullous congenital ichthyosiform erythroderma, Conradi syndrome, Sjogren-Larsson syndrome, Chanarin Dorfman syndrome (neutral lipid storage disease), Gaucher disease, trichothiodystrophy, and X-linked recessive ichthyosis. Approximately 65% of babies born with a collodion membrane have an associated autosomal recessive congenital ichthyosis. Once the membrane sheds, the underlying genetic condition manifests[3].

Spontaneously-healing collodion babies (SHCB) are also well documented in the literature. Approximately 10-20% of babies with collodion membranes clear spontaneously and develop normally, though often with mild ichthyosis[4]. Mutations in transglutaminase 1 (TGM1) and ALOX12B and ALOXE3 have been detected in this phenotype[2].

Interestingly, another variant of autosomal recessive ichthyoses has been termed "bathing suit ichthyosis." Affected individuals born with collodion membranes later develop brown lamellar scales restricted to bathing suit areas in the first few weeks of life. Areas such as the face and extremities typically are spared. The involved areas correlate with areas of the body with warmer temperatures. Exacerbations in warmer seasons and climates can occur. Mutations in TGM1 have also been identified in this phenotype.[5, 6]

Babies born with collodion membranes should be monitored in the NICU, in high-humidity incubators to prevent dehydration. Compromised barrier function can lead to increased transepidermal water loss and inability to thermoregulate. No clear guidelines exist on optimal incubator parameters; however most advocate humidity settings between 60-100%. Temperature settings are adjusted to maintain the infant's temperature in a normal range- both hypothermia and hyperthermia can result from collodion membranes. Electrolytes and fluid balance must be monitored due to risk of hypernatremic dehydration. There is an increased susceptibility to cutaneous infection and septicemia, and careful monitoring is imperative. Cardiopulmonary complications may include respiratory difficulty due to restriction of chest expansion and aspiration pneumonia.

The mainstay of treatment is aggressive application of emollients every 4 to 6 hours. Application of medicated ointments should be avoided due to risk of increased percutaneous absorption and systemic toxicity. Evaluation by ophthalmology for management of ectropion and by otolaryngology for management of ear canal obstruction may be necessary.

Diagnostic workup is limited in the acute setting. Genetics consultation may be beneficial. Other signs and symptoms may guide further genetic workup. Biopsy is typically not indicated in the acute setting, and may prove more useful once the membrane has shed and the underlying disorder manifests. Microscopic examination of hair with and without polarized light can provide further clues to underlying diagnoses.

REFERENCES

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6. Bathing suit ichthyosis with summer exacerbation: a temperature-sensitive case. Yamamoto M, Sakaguchi Y, Itoh M, et al. Br J Dermatol. 2012;166(3):672-4.

PRESENTERS

Eduardo K. Moioli, MD, PhD; Arlene Ruiz De Luzuriaga, MD; Kathleen Mullane, DO; Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS

A 65 year old female presented with "draining cysts" on the posterior thighs that had developed approximately 7 months prior. Lesions started to develop after being on a cruise ship, where she had been sitting in a hot tub. Lesions were located on the posterior right and left thighs, and started as nodules that progressed to larger plaques. Lesions were only mildly tender at the time of the initial presentation. Drainage from superficial skin openings on the areas of the plaques was predominantly clear in color. Patient denied fevers or chills.

PAST MEDICAL HISTORY

Systemic lupus erythematosus, discoid lupus (scalp), basal cell carcinoma, seborrheic dermatitis, heart failure with preserved ejection fraction, hypertension, sleep apnea, hyperuricemia

FAMILY HISTORY

Non-contributory

MEDICATIONS

Methylprednisone, hydroxychloroquine, metoprolol-XL, folic acid, pyridoxine, amlodipine, aspirin

ALLERGIES

Penicillin (rash), sulfamethoxazole-trimethoprim (hives)

PHYSICAL EXAMINATION

On physical exam the patient had scattered well-demarcated, violaceous, indurated ovoid plaques of 3-5cm in the widest dimensions on the bilateral upper posterior thighs with draining sinus tracts opening onto the skin surface. No tenderness or fluctuance was appreciated.

DERMATOPATHOLOGY

Initial biopsy: Right Upper Inner Thigh Plaque: Epidermal hyperplasia, focal hyperkeratosis, mixed inflammatory infiltrate with histiocytes, plasma cells, and neutrophils was seen. Bacterial, fungal, mycobacterial, treponemal pallidum studies were negative. Polarized light exam was negative for birefringent foreign material.

Subsequent biopsy: Left Intergluteal Plaque (~6 months after initial presentation): Psoriasiform hyperplasia and focal hyperkeratosis; mixed dermal inflammatory infiltrate with numerous plasma cells. Bacterial, fungal, mycobacterial, treponemal pallidum studies negative.

LABORATORY DATA (abnormal findings are in **bold**)

Complete blood count: **Leukocytes 11.4 K/µL** (3.5-17.7), hemoglobin 14.5 g/dL (9.8-17.6), platelets 285 K/µL (150-450)

Differential: Neutrophils 79%, lymphocytes 13%, monocytes 7%, eosinophils 1%

Comprehensive Metabolic Panel: Sodium 138 (134-149 mEq/L), Potassium 3.6 (3.5-5.0 mEq/L), Chloride 96 (05-108 mEq/L), Carbon Dioxide 27 (23-30 mEq/L), **BUN 42 (7-20 mg/dL), Creatinine 1.6 (0.5-1.4mg/dL)**, Calcium 10.6 (8.4-10.2 mg/dL), Alkaline phosphatase 71 (50-150 U/L), AST 22 (8-37 U/L), ALT 18 (8-35 U/L)

ESR 61 (1-50 mm/hr)

CRP 18 (<5 mg/L)

SSA 56 (<20)
SSB neg
DNA neg
ANA 160 (speckled)
C3 169 (83-188mg/dL)
Anti-Sm neg
IgA within normal limits
IgG within normal limits
RF neg
Quantiferon gold neg
CMV neg
AFB neg

Initial Tissue Culture: Negative for fungi, bacteria, and mycobacteria.
Initial Wound drainage culture: **Corynebacterium species (2 strains)**
Subsequent Tissue Culture (~6 month after initial presentation): **Broth with Actinomyces neuii growth** (Resistant to clindamycin, Susceptible to penicillin), Negative for fungi and mycobateria.
Subsequent Wound drainage culture (~6 months after initial presentation): >4 strains of aerobic gram positive organisms (negative for S. aureus, P. aeruginosa, beta streptococcus groups A or B, and enterococci)

DIAGNOSIS
Actinomyces neuii skin infection

TREATMENT AND COURSE
Given concern for deep tissue infection on bilateral posterior thighs at initial presentation, the patient was started on Ciprofloxacin 250mg PO bid x 7d, Gentamycin 0.1% ointment in the mornings, and Mupirocin 2% ointment in the evenings noting patient's allergies to sulfa and penicillin. Once initial culture was positive for corynebacterium spp., clindamycin 1% gel daily was also added.

Given only minimal clinical improvement and continued wound drainage, the patient was started on doxycycline 100mg PO bid and continued topical clindamycin and mupirocin. Subsequently, drainage from plaques significantly improved, but patient discontinued doxycycline after approximately 5 months due to gastrointestinal intolerance, which led to recurring drainage starting within a month of discontinuation. Given clinical worsening, doxycycline was restarted for planned course of 6 weeks along with continuation of topical treatment as prior.

Despite initial improvement while on a repeat treatment of doxycycline, plaques subsequently became more tender and began to drain bloody discharge from some areas whereas other affected regions seemed to mildly improve. Patient was then started on 5 day course of Ciprofloxacin 250mg PO bid. Despite this course, wound drainage was persistent and a new indurated violaceous plaque with larger sinus tract opening draining serosanguinous yellow fluid on the left intergluteal region developed. This new plaque was biopsied for culture and staining, which showed *Actinomyces neuii* growth (results referenced above as ~6 months after initial presentation). Given the new bacterial organism isolated, the patient was treated with Doxycycline 100mg PO bid and Clarithromycin 250mg PO bid for 14 days, and Infectious Disease consult was obtained.

Given that the patient's history of penicillin allergy was vague, she was started on intravenous piperacillin after extensive discussion with the patient by Infectious Diseases colleagues. After initial improvement of the plaques and wound drainage, unfortunately, the patient developed fever, diarrhea, cough and was admitted to the hospital for drug fever after appropriate work-up. Piperacillin was

discontinued. Patient thereafter improved on Vancomycin while inpatient, however she declined new PICC line placement for long-term intravenous antibiotic administration. Patient was discharged on Ciprofloxacin 750mg PO bid and Azithromycin 500mg PO three times weekly. Plaques are currently gradually improving on the latter regimen with less drainage.

DISCUSSION

History and Taxonomy: Until relatively recently, *Actinomyces neuii* was grouped under the genus Coryneform group-1. In 1993, it was found that a subgroup of these catalase-positive, nitrate-reducing, non-motile coryneforms that were biochemically similar did not reduce nitrate. This distinguished subset of bacteria was referred to as CDC group 1-like Coryneform bacteria. Given some of these phenotypic differences among the Coryneform groups, further studies with comparative analysis of the rRNA sequence data of isolated Coryneform group-1 bacteria revealed that these bacteria were in fact more similar to the Actinomyces genus based on their 16s rRNA sequences. These new data led to the reclassification of these bacteria previously categorized as Coryneform group-1 as a distinct new species, *Actinomyces neuii*. Since its identification, *A. neuii* is now estimated to represent approximately 17% of all clinically relevant Actinomyces infections.

Infections: Although the *Actinomyces spp.* are known colonizers of the human body, *A. neuii* has been demonstrated in normal flora in only one study. Other Actinomycetes such as *A. israelii* are part of the normal flora of the oral cavity and, interestingly, *A. neuii* is most prominent in patients with gingivitis. Transmission from patient to patient has not been observed, except for one case of maternal chorioamnionitis resulting in neonatal septicemia. Most infections are thought to be due to an endogenous source. To date, however, there are no studies investigating the presence of *A. neuii* in the environment. These bacteria are not known to classically cause typical actinomycosis. The most frequent types of infections with *A. neuii* are actually abscesses and infected atheromas followed by other skin infections, endophthalmitis, and bacteremia. Few prior reports of skin infections with *A. neuii* have included similar presentations to the currently presented case. One other case of an intergluteal indurated cyst that drained purulent fluid is found in the literature. Fluid drained from infected sites may demonstrate either Gram-positive coryneform rods or no microorganisms at all, as seen in this case, making prompt identification of this organism in infected skin difficult. Repeated cultures of wound drainage or biopsied tissue may be necessary as observed here.

Treatment: Historically, the antimicrobial susceptibility of *A. neuii* is similar to that of other Actinomyces spp. Commonly, all strains have been reported to be susceptible to penicillins, cephalosporins, imipenem, rifampicin, vancomycin, erythromycin, and clindamycin. Variable resistance to tetracyclines, aminoglycosides, and ciprofloxacin has been reported. Antibiotics from the penicillin family tended to resolve *A. neuii* infections in previously reported cases of skin infections, and significant improvement had also been observed in the present case during administration of piperacillin. However, allergy to penicillin and resistance to clindamycin has proved to be a significant deterrent in the treatment of this patient.

The current presentation with slowly developing indurated, non-tender swelling of the skin with eventual purulent drainage through sinus tracts is more typical of Actinomycosis secondary to *Actinomyces israelli* and has not been classically reported for *Actinomyces neuii* infections. In addition to the paucity of well documented clinical signs, the similarity of this organism to Corynebacteria, as noted above, may lead to the frequent misinterpretation of these bacteria as a skin contaminant, hindering its prompt identification and appropriate treatment. It is prudent to speculate that the initial culture results for this patient which demonstrated Corynebacterium may have actually been *Actinomyces neuii* that was later identified in the subsequent biopsy. In addition, this is the first documented case of a clindamycin resistant strain to our knowledge. Whether resistance was present early or developed after long-term use of topical clindamycin remains unclear. It is also unclear

whether the immunosuppressed status of this patient contributed significantly to the unusual presentation and resistance to treatment.

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PRESENTERS

Min Deng, MD, Vesna Petronic-Rosic, MD, MSc, Diana Bolotin MD, PhD, Christopher R. Shea MD

UNKNOWN

CASE 6

PRESENTERS

Sonya Kenkare MD, Min Deng, MD, Arlene Ruiz de Luzuriaga, MD, MSc, Maria Tsoukas, MD, PhD

HISTORY OF PRESENT ILLNESS

48 year old Caucasian female s/p exploratory laparotomy in April 2012 that revealed mesenteric fibromatosis. Two months after she was started on sorafenib for treatment of mesenteric fibromatosis she began to notice tender rough skin lesions that began around the knees, but gradually spread to the upper and lower extremities including the palms and soles.

PAST MEDICAL HISTORY

Fibromatosis, anemia

FAMILY HISTORY

Colon cancer- sister at age 37 and maternal grandfather. No personal or family history of non-melanoma skin cancer.

MEDICATIONS

Sorafenib, ferrous sulfate, Sulindac

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

Extensive ~3-8 mm pink-to-violaceous firm, tender papules with hyperkeratotic central crust, distributed throughout the lower extremities and upper extremities, including 2 yellow firm papules (~2 mm) on left palm and 4 firm yellow papules (~ 4 mm) on left sole.

DERMATOPATHOLOGY

Four shave and punch biopsies from the right arm and left leg showed keratinocytes with severe cytologic atypia present in the epidermis consistent with squamous cell carcinoma in situ for all biopsied lesions.

LABORATORY DATA

None

DIAGNOSIS

Eruptive squamous cell carcinomas secondary to sorafenib chemotherapy

TREATMENT AND COURSE

Upon discussion with oncology, the decision was made to hold sorafenib. Due to the extent of involvement cryotherapy was used for selected lesions and field therapy with topical 5-fluorouracil (5-FU) under occlusion was attempted. Significant improvement of the SCCs has been noted with topical 5-FU chemotherapy wraps.

DISCUSSION

Sorafenib is a multikinase inhibitor (MKI) chemotherapy with inhibitory action over VEGFR, PDGFR and tyrosine kinase and Raf kinases. It is often used to treat renal cell carcinoma and hepatocellular carcinoma. In our patient, sorafenib was used to treat fibromatosis.

Sorafenib is associated with several systemic side effects, including diarrhea, nausea, fatigue,

hypertension and cutaneous manifestations in up to 93% of patients. The most common cutaneous toxicities reported with the use of sorafenib include generalized erythematous eruptions including hand-foot skin reactions in greater than 50% of patients, androgenic-like alopecia in 27%, subungual hemorrhage (60-70%) and facial erythema (63%.) Multiple cutaneous SCCs have been reported in 7-15% of patients on sorafenib. These side effects may represent "off-target" effects of this presumably "targeted therapy."

In contrast to similar MKIs, sorafenib is a pan-RAF inhibitor. A possible mechanism for the increased number of epithelial skin cancers in the setting of RAF-inhibition might be a paradoxical activation of mitogen-activated protein kinase (MAPK) signaling on keratinocytes with an activated or mutated RAS gene. RAS mutations have been identified in the keratinocytes of sun damaged skin and actinic keratoses, a known precursor lesions to SCC.

Ultraviolet radiation can induce RAS mutations in keratinocytes, but these mutations are usually not sufficient to induce malignant transformation. Similarly, the increase in cutaneous malignancies is unlikely to be due to a direct mutagenic effect of RAF inhibition. Most likely, the interaction between RAF inhibition and RAS mutant keratinocytes leads to an overwhelming proliferation of abnormal cells leading to subsequent KAs and SCC.

Of note, BCC was rarely noted in patients on MKIs. In one study, a BCC was noted with a focus of squamous metaplasia. In the literature recurrence of SCC was reported rarely and cutaneous malignancies were not aggressive in nature. Depending on the application of the MKI, continued treatment through cutaneous malignancy may be reasonable with appropriate dermatologic follow up.

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PRESENTERS

Duri Yun, MD, MPH, Arlene Ruiz de Luzuriaga, MD, MPH and Maria Tsoukas, MD, Ph.D

HISTORY OF PRESENT ILLNESS

The patient is a 63 year-old female with a history of stage III sporadic metastatic medullary thyroid cancer, status post total thyroidectomy with central neck dissection and subsequent lateral neck dissection for recurrent disease, fifteen months after her initial diagnosis. Five months prior to presentation in dermatology, her cancer was complicated with metastatic lung disease and was treated with cabozantinib, a tyrosine kinase inhibitor. She was seen in our clinic for evaluation of painful nodules on her scalp and abdomen. These cutaneous symptoms initially began as a tingling sensation within her scalp, approximately two months prior to her visit. Her treatment course with cabozantinib had been complicated by gastrointestinal side effects and the patient had initially assumed that the skin symptoms were another adverse reaction to the medication. Due to the severity of the gastrointestinal side effects and in light of undetectable calcitonin levels in her blood work, she was started on a drug holiday two weeks following the onset of her scalp symptoms. Upon presentation six weeks later, her gastrointestinal symptoms had resolved, however her skin paresthesias had evolved to become painful nodules on her scalp and abdomen.

PAST MEDICAL HISTORY

Hashimoto's thyroiditis, sporadic medullary thyroid cancer Stage III diagnosed in March 2011

FAMILY HISTORY

Hashimoto's thyroiditis in sister
No family history of thyroid cancer
Myocardial infarction in father

MEDICATIONS

Synthroid, Lomotil prn

ALLERGIES

Meperidine

PHYSICAL EXAMINATION

Approximately 5-10 scattered, very firm, exquisitely tender subcutaneous nodules are present on the scalp, temple and abdomen ranging in size from 1-1.5 cm in diameter. There is mild to moderate overlying erythema. No overlying scaling or surrounding erythema is noted.

DERMATOPATHOLOGY

Posterior scalp: Sections are of skin with collections of round to oval neoplastic cells in the dermis arranged in a nested pattern and in cords between collagen bundles, with moderate pleomorphism. Several mitotic figures are identified.

Left upper abdomen: Sections are of skin with a dermal proliferation of round to oval neoplastic cells with moderate pleomorphism. The neoplastic cells are organized in sheets and linear cords, and are separated by thickened, sclerotic collage bundles. Numerous mitotic figures are identified.

Immunohistochemical staining on both specimens revealed strong and diffuse immunolabeling of the neoplastic cells with anti-AE1/AE3 antibody, anti-thyroid transcription factor-1 antibody, anti-synaptophysin antibody, anti-chromogranin antibody.

Immunohistochemical staining on both specimens revealed weak immunolabeling of the neoplastic cells with anti-calcitonin antibody.

LABORATORY DATA

The following were negative or within normal limits:
Calcitonin: <5 pg/mL (<8)
Carcinoembryonic antigen: 2.9ng/mL (0-3.4)
Thyroid stimulating hormone: 1.19 mcU/mL (0.30-4.00)
Complete blood count: Leukocytes 6.6K/µL (3.5-11), hemoglobin 12.9g/dL (11.5-15.5), platelets 278K/µL (150-450)
Differential: Granulocytes 72%, lymphocytes 15%, monocytes 12%, eosinophils 1%, basophils 0%
Comprehensive metabolic panel: Glucose 96mg/dL (60-109), sodium 140mEq/L (139-149), potassium 4.2mEq/L (3.5-5.0), chloride 104mEq/L (95-108), carbon dioxide 27mEq/L (23-30), anion gap 9mmol/L (6-15), blood urea nitrogen 9mg/dL (7-20), creatinine 0.6mg/dL (0.5-1.4), GFR estimate 101mL/min/BSA (>59), calcium 9.7mg/dL (8.4-10.2), total bilirubin 0.4mg/dL (0.1-1.0), total protein 6.8g/dL (6.0-8.3), albumin 4.4g/dL (3.5-5.0), alkaline phosphatase 38U/L (50-150), aspartate aminotransferase 16U/L (8-37), alanine aminotransferase 12U/L (8-35)
RET proto-oncogene: a mutation was not detected

DIAGNOSIS

Metastatic medullary thyroid cancer

TREATMENT AND COURSE

The patient was restarted on cabozantinib at a lower dose of 60 grams daily and oral analgesics to manage the pain of the nodules. She declined offers to resect the nodules. Tramadol has been effective and she is following with pain clinic.

Recently, she has stopped cabozantinib due to lack of clinical response and was switched to another tyrosine kinase inhibitor, vandetanib.

DISCUSSION

Thyroid medullary carcinoma is an uncommon tumor of the neuroendocrine parafollicular C cells of the thyroid that accounts for less than 4% of all thyroid cancers in the United States.[1] Fifty-six percent of the cases are considered sporadic, as was the case for this patient. The rest of the cases are attributed to familial medullary thyroid carcinoma (22%) and multiple endocrine neoplasia (MEN) syndromes, MEN 2A (15%) and MEN 2B (7%).[2] Cutaneous metastases of thyroid medullary cancer are even more rare as only 16 cases have been reported in the literature.[3-10] Generally, thyroid medullary carcinoma is considered an aggressive cancer with regional lymph node metastases being present in up to 80% of all patients with a primary tumor of at least 1 cm diameter.[4] However, this cancer has a moderate prognosis with a 78.2% survival rate at 5 years and 65% at 10 years.[11] Independent prognostic factors associated with a poor prognosis include age greater than sixty-five years and distant tumor stage, of which this patient had the latter.[11]

Treatment of medullary thyroid cancer has mainly been surgical with total thyroidectomy and regional lymph node dissection with or without regional radiation therapy depending on tumor stage.[1] Management guidelines recommend following calcitonin levels as this is a sensitive biomarker of primary and metastatic disease.[1] More recently, tyrosine kinase inhibitors associated with multiple receptors specific to medullary thyroid cancer have been used in management of progressive disease.[12] Our patient was treated with cabozantinib which targets tyrosine kinases involving vascular endothelial growth factor (VEGF) receptor 2, hepatocyte growth factor (MET) and RET pathways.[12]

Of note, the calcitonin staining on dermatopathology review was weakly positive, which correlated with the undetectable calcitonin levels the month prior to her biopsy. A review of her medullary thyroid cancer course revealed that she had originally presented with a rather low calcitonin level of 68 pg/mL compared to the stage III disease burden found at the time of thyroidectomy and node dissection.[1] Also, her initial pathologic exam at the time of thyroidectomy had shown strong but patchy calcitonin positivity on immunohistochemical staining. With these findings, it appears that she has a variant of medullary thyroid cancer in which there is no marked elevation of calcitonin. This variant has been shown to be more aggressive. [13]

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PRESENTERS
Mara Beveridge, MD, Vesna Petronic-Rosic, MD, MSc, Maria Tsoukas, MD, PhD

HISTORY OF PRESENT ILLNESS
The patient is a 34 year-old African American woman with a past medical history significant for kidney-pancreas transplant due to complications of Type I diabetes mellitus. Now on hemodialysis after failure of kidney allograft, who presents with painful nodules on the bilateral shins for 2 weeks duration. She denies any new medications and has a negative personal and family history of sarcoidosis.

PAST MEDICAL HISTORY
Type I diabetes mellitus, simultaneous kidney-pancreas allograft transplantation in 2007, prograf-induced TTP (thrombotic thrombocytopenic purpura) resulting in failure of kidney allograft in 2009

PAST SURGICAL HISTORY
Kidney and pancreas transplant in 2007, nephrectomy of transplanted kidney in 2010

FAMILY HISTORY
Non-contributory

MEDICATIONS
Cyclosporine, prednisone, valacyclovir (prophylaxis), amlodipine, calcium acetate, epoetin alfa, ergocalciferol, sensipar, docusate

ALLERGIES
Ciprofloxacin, gentamicin, leflunomide, tacrolimus, vancomycin

PHYSICAL EXAMINATION
Multiple violaceous, tender, deep nodules scattered over the anterior shins bilaterally; each was 4-6 cm in diameter.

DERMATOPATHOLOGY
Left lateral shin biopsy: sections are of skin and subcutaneous tissue with septal panniculitis and an area of enzymatic fat necrosis with ghost cells and neutrophilic infiltrate.

LABORATORY DATA
Complete blood count: Leukocytes 7.5 K/uL (3.5-11), hemoglobin 10.1 g/dL (11.5-15.5), platelets 346 K/uL (150-450)

Basic metabolic panel: Glucose 120 mg/dL (60-109), sodium 138 mEq/L (134-149), potassium 3.7 mEq/L (3.5-5.0), chloride 95 mEq/L (95-108), carbon dioxide 30 mEq/L (23-30), blood urea nitrogen 19 mg/dL (7-20), **creatinine 4.8 mg/dL** (0.5-1.4; patient's baseline 3.8-14.6), calcium 8.8 mg/dL (8.4-10.2), phosphate 1.9 mg/dL (2.5-4.4)

Other chemistry: **Amylase 650 U/L** (28-100**), lipase 2893 U/L** (11-65; patient's baseline 130-300), **cyclosporine trough <30 ng/mL** (100-200)

Infectious disease: no cytomegalovirus DNA detected

DIAGNOSIS
Pancreatic panniculitis in a kidney-pancreas transplant patient

TREATMENT AND COURSE

The transplant team was contacted immediately upon receipt of the dermatopathology results. Laboratory data above was collected and the patient's cyclosporine dose was increased from 75mg PO BID to 100mg PO BID with close laboratory follow up. Over the next month her lipase trended downwards and returned to baseline (lipase 169) after 8 weeks. The patient did not require hospitalization at any point during this period.

DISCUSSION

Pancreatic panniculitis is a rare condition reported in up to 2% of patients with pancreatic disease, especially acute and chronic pancreatitis and pancreatic carcinoma. Pancreatic enzymes such as lipase, amylase, and tryptase when released, enter the circulation and can hydrolyze neutral fat to free fatty acids and glycerol at distant sites; thus resulting in the pathognomonic "ghost cells" that are seen histopathologically. Venous stasis is thought to play a role in the predilection of these lesions for legs; although, other involved sites such as abdomen, chest, arms, and scalp have been reported.

To the best of our knowledge this is the fifth case of pancreatic panniculitis reported in a transplant recipient, the second in a simultaneous kidney-pancreas transplant, and the first to be managed in the outpatient setting. Previously reported cases include, two kidney transplant recipients, one simultaneous kidney-pancreas recipient, and one pancreas-after-kidney transplant. As in our patient, all presented with classic painful deep nodules on the legs and all but one lacked significant abdominal symptoms. In the three patients that the transplanted organ was biopsied there was evidence of moderate to severe acute organ rejection and these patients responded positively to increased immunosuppression. Thus suggesting that when pancreatic panniculitis is seen in a transplant patient, organ rejection should be strongly considered as the underlying etiology and dermatologic manifestations are often the first sign and sometimes only sign.

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PRESENTERS
Alex Means, MD, Min Deng, MD, Monique Kamaria, MD, Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS
A 47 year old Caucasian male presented to dermatology with a pruritic eruption on his bilateral arms, buttocks, face, and axillae for one year. The lesions were refractory to emollient use. He was recently seen by an outside allergist in January 2013 who performed prick testing that was positive for pine oil and feline/equine products. The patient lives with two cats and lives near a horse farm.

PAST MEDICAL HISTORY
Patient has a history of lactose intolerance with chronic diarrhea, bloating, and gas; obesity s/p gastric bypass surgery (roux-en-y gastroenterostomy) with 100lb weight loss, type 2 diabetes, gout, L knee replacement. He has never smoked and drinks 2-3 alcoholic drinks a week.

FAMILY HISTORY
Eczema in brother, asthma in son

MEDICATIONS
Loratadine, multivitamin, trazodone, venlafaxine ER

ALLERGIES
No known drug allergies but has allergies to pine oil and feline/equine products (per prick testing)

PHYSICAL EXAMINATION
47 year old male with multiple excoriated papules coalescing into plaques on bilateral dorsal hands, ventral wrists, scalp, posterior neck, buttocks, extensor elbows/knees, axillae, and R posterior calf. 1 intact vesicle on R dorsal hand.

DERMATOPATHOLOGY
There are subepidermal microvesicles and neutrophils within dermal papillae, as well as a superficial perivascular and interstitial infiltrate of lymphocytes and neutrophils. Direct immunofluorescence showed deposition of IgA in a speckled pattern in the dermal papillae.

LABORATORY DATA
Complete blood count: leukocytes 7.9 K/µL (3.5-11), hemoglobin 13.7g/dL (13.5-17.5), MCV 89.1fL (81-99), platelets 284 K/µL (150-450).
Differential: Neutrophils 57% (39-75), lymphocytes 32% (16-47), monocytes 6% (4-12), eosinophils 5% (0-7), basophils 0% (0-2).
Comprehensive metabolic panel: glucose 89mg/dL (60-109), sodium 141mEq/L (134-149), potassium 3.8mEq/L (3.5-5.0), chloride 106mEq/L (95-108), carbon dioxide 22mEq/L (23-30), anion gap 13mmol/L (6-15), BUN 21mg/dL (7-20), creatinine 1.0mg/dL (0.5-1.4), calcium 8.2mg/dL (8.4-10.2), total bilirubin 0.2mg/dL (0.1-1.0), total protein 6.7g/dL (6.0-8.3), albumin 4.3g/dL (3.5-5.0), alk phos 113U/L (30-120), AST 20U/L (8-37), ALT 23U/L (8-35)
Tissue Transglutaminase IgA: Ab 19 units (normal < 20, weak positive 20-30, positive > 30)
Endomysial IgA Ab: negative (no range provided)
Total IgA: 343mg/dL (100-490)
G6PD quantitative: 10.6 (8.8 to 13.4 U/g Hb)

DIAGNOSIS
Dermatitis herpetiformis with negative anti-endomysial and anti-tissue transglutaminase antibodies

TREATMENT AND COURSE

Patient was started on clobetasol 0.05% ointment twice a day for 2 weeks and then changed to triamcinolone 0.1% ointment PRN with significant improvement. He was referred to gastroenterology in April at which time an enterogastricduodenoscopy (EGD) was performed. The EGD was significant for a jejunum and gastrojejunostomy with scalloped and fissured mucosa, with patchy mild to moderate villous blunting but no significant increase in intraepithelial lymphocytes or crypt hyperplasia. Labs at that time were remarkable for:

Repeat anti-endomysial Ab: negative
Repeat anti-tTG Ab: 22 (normal < 20, weak positive 20-30, positive > 30)
Deamidated gliadin IgA: 275 units (< 20 negative, 20-30 weak positive, > 30 positive)
Deamidated gliadin IgG: 93 unites (< 20 negative, 20-30 weak positive, > 30 positive)
HLA typing: DQA1* negative for DQ8, DQB1* positive for DQ2

DISCUSSION

Dermatitis herpetiformis (DH) is an autoimmune disease found in association with celiac disease (CD) and characterized by granular IgA deposition in the skin. The primary autoantigen in DH is epidermal transglutaminase (eTG), while in celiac disease it is tissue transglutaminase (tTG). The gold standard for diagnosis is detection of granular deposits of IgA within the papillary dermis via direct immunofluorescence of perilesional skin and with subepidermal cleft formation occurring within the lamina lucida on EM. This leads to a predominantly neutrophilic infiltrate and results clinically in vesicle formation, the hallmark of DH, classically involving the symmetric extensor surfaces of the upper and lower extremities, scalp, nuchal area, and buttocks. It is found more commonly in individuals of Northern European descent, with prevalence rates comparable to other immunobullous disease—around 11.2/100,000 people. Males are affected twice as often as females. Treatment of DH involves maintenance of a gluten-free diet, with subsequent disappearance of IgA immune complexes and anti-eTG titers. Alternatively, dapsone and topical steroids can be used for interim or permanent control.

tTG is a ubiquitously expressed cytoplasmic, calcium-dependent enzyme that catalyzes crosslinks between glutamine and lysine protein residues. eTG is primarily found in basal keratinocytes and dermal capillaries and shares conserved epitopes with tTG. In DH, tTG modifies the alcohol-soluble fraction of gluten known as gliadin into an autoantigen with stronger affinity for HLA-DQ2 on antigen-presenting cells (APCs), resulting in T-cell stimulation and inflammation. Virtually all patients with DH carry the HLA-DQ2 or HLA-DQ8 alleles, and the absence of these alleles has a very strong negative predictive value for diagnosis of DH. Gliadin is the alcohol-soluble part of gluten that is only partially digested in the gut, with subsequent modification by tTG via transamidation or deamidation reactions or cross-linking to tTG, resulting in more allergenic properties of these digestion-resistant peptides.

Detection of anti-tTG IgA for diagnosis DH is almost 90% sensitive, while that of anti-eTG IgA is almost 95%. Anti-endomysial (EMA) IgA tests for a variant of tTG found in endomysium and is similarly sensitive for more than 90% of pts with DH. There are reports of patients with seronegativity to both anti-EMA and anti-tTG antibodies, possibly because of the similarity of their target antigens. Anti-gliadin antibodies are not specific for DH and are not recommended as screening tests, though a recent study suggests that deamidated peptide assays may have sensitivity for DH of 90%. The duodenum is considered to be the highest source of the tTG Ab, which may explain why it was negative in this patient. Alternatively, patients with mild inflammation of their small intestine can manifest negative serologies.

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PRESENTERS
Sogyong Auh MD, PhD, Christopher R. Shea MD, and Diana Bolotin MD, PhD

HISTORY OF PRESENT ILLNESS
A 33-year-old female with stage IV M1c metastatic melanoma presented for evaluation of tender, erythematous, and violaceous macules and edematous nodules on the extremities. The patient had been diagnosed with melanoma, superficial spreading type (Breslow thickness 0.86 mm, Clark level III, focal ulceration, rare mitotic figures, vertical growth phase, no vascular invasion) of the left lateral back in 1998. She was treated with wide local excision with negative margins, without lymph node biopsies. She presented 14 years later with sudden back pain and a subcutaneous left breast lump and was found to have metastatic melanoma lesions in the brain, right lung, abdominal wall, left kidney, and pelvis. The presence of a *BRAF* V600E mutation was confirmed and vemurafenib was initiated. The cutaneous nodules developed first on her arms, then legs, about 3 weeks after starting vemurafenib. She denied fevers, chills, or joint pains.

PAST MEDICAL HISTORY
Metastatic melanoma

FAMILY HISTORY
Non-contributory

MEDICATIONS
Vemurafenib, dexamethasone, hydroxyzine, loratadine, ondansetron, omeprazole, Senokot, triamcinolone ointment

ALLERGIES
Sulfa

PHYSICAL EXAMINATION
Scattered erythematous and violaceous, blanchable 5-6 mm macules and slightly edematous nodules were present on the bilateral arms and legs. A firm violaceous subcutaneous nodule (previously diagnosed metastatic lesion) was present on the left breast, with significant reduction in size compared to prior exam.

DERMATOPATHOLOGY
4-mm punch biopsies from the left lower leg and right upper arm showed a neutrophilic lobular panniculitis, with foci of neutrophils present in the lobules of subcutaneous fat and with surrounding lipomembranous change. The periodic acid-Schiff stain was negative for fungi or significant basement membrane thickening. The methenamine silver, gram, and fite stains were negative for fungi, bacteria, and mycobacteria respectively.

LABORATORY DATA
Antinuclear antibody: 40 (0-80)
Antineutrophil cytoplasmic antibodies <20
Rheumatoid factors: 13IU/mL (< 14)

DIAGNOSIS
Vemurafenib-induced neutrophilic panniculitis

TREATMENT AND COURSE

Based on reported cases, treatment with ibuprofen on an as-needed basis was recommended. However, the patient felt that the lesions were resolving without treatment and declined. She was continued on the same dose of vemurafenib (960 mg BID). A few weeks later she developed an acute febrile illness, with joint aches, sore throat, and episodes of nausea and emesis. She was evaluated by hematology-oncology and treated with Augmentin 875-125 mg BID for 1 week. Vemurafenib (960 mg BID) was held until she improved and then restarted at a lower dose of 720 mg BID. The rash recurred but resolved quickly without treatment.

DISCUSSION

While the treatment of metastatic malignant melanoma remains challenging, recent advances have been promising. The discovery in 2002 of activating mutations in the serine/threonine kinase gene *BRAF* in approximately 50% of melanomas led to development of the BRAF-inhibiting agents vemurafenib and dabrafenib. Various mutations in the *BRAF* gene have been described, but 80% of mutations result in substitution of glutamic acid (E) for valine (V) in codon 600, the *BRAF* V600E mutation.[1] Other common *BRAF* mutations include V600K (16%) and V600D/R (3%). These mutations lead to a BRAF protein that is constitutively active, ultimately resulting in unchecked proliferation and resistance to apoptosis, although the development of melanoma requires acquisition of additional mutations.[2]

Vemurafenib is indicated for adults with unresectable or metastatic melanoma harboring the *BRAF* V600E mutation. A phase III trial comparing vemurafenib with dacarbazine showed a statistically significant 56% overall survival benefit for vemurafenib over dacarbazine; objective response rates were 48% and 5%, respectively.[3] Common adverse effects associated with vemurafenib include fatigue, arthralgia, and dermatologic side effects including drug eruptions, squamous cell carcinomas, especially of keratoacanthoma (KA) type, and photosensitivity.[3,4] More recently, neutrophilic panniculitis associated with vemurafenib has been reported.[6-10] Reported cases have shown a female predominance and onset as early as 7 days or up to 7 weeks after starting BRAF inhibitor therapy. Often there are no associated symptoms, but some reports have described an association with arthralgias of varying severity. Histopathology typically demonstrated lobular neutrophilic panniculitis without vasculitis, although vasculitis was reported in 2 cases.[6,10] In most cases, the panniculitis resolved without cessation of vemurafenib treatment, although it was sometimes necessary to reduce the BRAF inhibitor dose. Spontaneous recovery did occur, and treatment, if needed, was limited to NSAIDs. Prednisolone was used to treat one case complicated by severe arthritis and vasculitis. Although one report required discontinuation of vemurafenib secondary to recurring panniculitis, the overall recommendation based on reported cases, is to manage symptoms with NSAIDS and continue vemurafenib therapy.

The mechanism by which BRAF inhibitors induce panniculitis is unclear. Some patients have exhibited elevation of markers of systemic inflammation such as CRP and ESR. Interestingly, the incidence of panniculitis does not appear to be influenced by combination treatment with BRAF and MEK inhibitors. Most of the patients who developed a panniculitis demonstrated at least an initial reduction in tumor burden with BRAF inhibitor treatment. However, as the number of reported cases is limited, it is not possible to assess whether development of panniculitis could be used as a surrogate marker for response to treatment.

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PRESENTERS

Adena E. Rosenblatt MD, PhD, Vesna Petronic-Rosic, MD, MSc, and Bernhard Ortel, MD

HISTORY OF PRESENT ILLNESS

A 43-year-old African American female presented to dermatology clinic in February 2012 with a 2.5 year history of painful plaques on both feet. As per patient, she had a biopsy of the lesions by an outside dermatologist that was consistent with psoriasis. She reports that the lesions were treated with phototherapy, acitretin, and clobetasol 0.05% ointment prior to presentation with some improvement but without resolution. After her initial visit at University of Chicago, she was started on acitretin 25mg daily and PUVA 2-3 times per week. At her 1-month follow up appointment she had some improvement but was taken off acitretin after developing headaches. She continued PUVA treatment with minimal improvement until June 2012 when she decided to discontinue the treatment. Over the next 3 months, she had progressive worsening with increase in size and pain to the extent that she could no longer ambulate. She also admitted to excoriating and manipulating the lesions. Of note, the patient worked as a truck driver transporting chemicals. A biopsy was performed in September 2012.

PAST MEDICAL HISTORY

Patient's past medical history is significant for hypertension, uterine fibroids s/p hysterectomy, L4-L5 radiculopathy, and latent tuberculosis (positive quantiferon gold in 3/2012) s/p INH treatment completed in 5/2013.

FAMILY HISTORY

No family history of cutaneous disease or cancer.

MEDICATIONS

Gabapentin, hydrochlorothiazide, Vicodin PRN

ALLERGIES

Fish Oil

PHYSICAL EXAMINATION

A 43-year-old African American female with symmetric, well-demarcated, hyperkeratotic plaques on the bilateral posterior plantar feet. Furthermore, there was a large exophytic verrucous plaque with overlying focal areas of hemorrhagic crust within the hyperkeratotic plaques.

DERMATOPATHOLOGY

The epidermis is composed of acanthotic downgrowths of well-differentiated squamous epithelium extending into the dermis. The base of the rete pegs have a bulbous appearance. There are invaginations within the epidermis filled with parakeratotic horn. In situ hybridization for high risk HPV was negative and for low risk HPV was negative.

LABORATORY DATA

Quantiferon gold: positive
HIV: negative

IMAGING STUDIES

MRI of feet: Marked abnormal thickening of the cutaneous plantar soft tissue and subcutaneous layer without extension to the plantar fascia, muscle, tendon, or bones.

DIAGNOSIS

Bilateral verrucous carcinoma of the plantar feet

TREATMENT AND COURSE

The patient had a complete wide excision of the bilateral verrucous carcinoma with placement of a left gracilis muscle graft to the right foot and bilateral split thickness skin grafts by plastic surgery in February 2013. She had significant improvement at her follow up appointment in May 2013 but had thick callus formation. A follow up biopsy at that time was negative for verrucous carcinoma.

DISCUSSION

Verrucous carcinoma also known as carcinoma cuniculatum is a rare, low-grade variant of squamous cell carcinoma. The incidence is 1-3 per million and accounts for 0.6% of head and neck cancers. It commonly affects men over 50 years old. The tumor can be locally aggressive penetrating down to the subcutis, fascia and bone but has a very low potential for metastasis (1). The tumors are usually well-demarcated exophytic, papillomatous proliferations.

There are three major subtypes of verrucous carcinoma based on location. The first subtype is epithelioma cuniculatum, which usually occurs on the plantar surface of the foot. The second is giant condyloma acuminatum of the genitalia also known as Buschke-Lowenstein tumor (2). The third is oral florid papillomatosis also known as Ackerman tumor, which occurs in the oral mucosa and is the most common type (2). The palate, buccal mucosa, and alveolar process are frequently involved. Verrucous carcinoma can arise from proliferative verrucous leukoplakia in the oral mucosa.

The pathophysiology of verrucous carcinoma is still unclear. It is possibly related to chronic inflammation and ulceration. Lesions have been reported to arise in sites of prior trauma, scars, amputation stumps, osteomyelitis fistulae and in patients with chronic venous insufficiency. Verrucous carcinoma can be associated with HPV infections particularly of subtypes 6b, 11, 16, and 18. Oral mucosal lesions have also been linked to smoking and chewing tobacco (1).

The histopathology is characterized by hyperkeratosis and acanthosis with a papillary surface and deep bulbous rete ridges (2). The epithelium is well differentiated with few mitotic figures and minimal atypia. About a quarter of verrucous carcinomas have foci of typical squamous cell carcinoma. Immunostaining can be performed to differentiate verrucous carcinoma from traditional squamous cell carcinoma. Both carcinomas stain positively for bcl-2, Ki-67, and p53; however, p53 and Ki-67 stain positive in the lower third of the epidermis in verrucous carcinoma compared to the full thickness of the epidermis in squamous cell carcinoma (2).

The definitive treatment is wide surgical excision. Mohs micrographic surgery is another therapeutic option (3). Adjuvant treatment with imiquimod 5% cream to shrink the tumor prior to surgical excision has been reported to be effective (4). Systemic retinoids, specifically acitretin has also been used for treatment of multiple verrucous carcinomas (5). Radiation therapy is not used due to concerns for possible anaplastic transformation.

There are only two reported cases of bilateral verrucous carcinoma of the plantar feet in the literature (6, 7).

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PRESENTERS
Monique Kamaria, MD, Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS
A 20 year-old healthy Caucasian male presented for evaluation of erythematous lesions on the trunk and extremities. The lesions were gradually expanding in size and increasing in number over a period of two weeks. The lesions were asymptomatic. During this time, he also experienced a few subjective fevers. He reported a history of frequent biking through the woods, but did not recall any history of bug bites. He lives in Boston, where he attends college. He denies any new medications or any changes to his skin care regimen or other products.

PAST MEDICAL HISTORY
None

FAMILY HISTORY
None

MEDICATIONS
None

ALLERGIES
Penicillin

PHYSICAL EXAMINATION
Numerous erythematous annular patches with central clearing scattered across the trunk and extremities, ranging in size from 5-20 centimeters. No overlying scale. No visible arthropod bite. No mucosal involvement. No facial or palm and sole involvement.

DERMATOPATHOLOGY
None

LABORATORY DATA
Complete blood count: Leukocytes 10.7 K/µL (3.5-11), hemoglobin 14.3 g/dL (13.5-17.5), platelets 286 K/µL (150-450)
Differential: Neutrophils 72%, lymphocytes 20%, monocytes 6%, eosinophils 1%
Complete metabolic panel: Glucose 91 mg/dL (60-109), sodium 138 mEq/L (134-149), potassium 4.4 mEq/L (3.5-5.0), chloride 99 mEq/L (95-108), carbon dioxide 27 mEq/L (23-30), BUN 10 mg/dL (7-20), creatinine 1.2 mg/dL (0.5-1.4), total bilirubin 1.2 mg/dL (0.1-1.0), albumin 4.6 g/dL (3.5-5.0), AST 17 U/L (8-37), ALT 15 U/L (8-35), alk phos 55 U/L (30-120)
Lyme Ab titer: 4.10 (< .75 EIA)
Lyme IgG immunoblot: negative
Lyme IgM immunoblot: positive

DIAGNOSIS
Disseminated erythema chronicum migrans/Lyme disease

TREATMENT AND COURSE
The patient was started on a course of doxycycline 100mg po twice daily for 2 weeks for Lyme disease. Laboratory confirmation was obtained thereafter. The patient completed the course and had resolution of symptoms. He was not able to return for follow up.

DISCUSSION

Erythema chronicum migrans represents the initial cutaneous manifestation of lyme disease, the most common tick-born illness in the United States. It is an infection of the *Borrelia* genus of spirochetes transmitted by bites from Ixodes, or less commonly Amblyomma, ticks. Lyme disease has a worldwide distribution, but is most common in the US and Europe. An estimated 300,000 cases are reported in the U.S. annually[1]. In the US, *B. Burgdorferi* is the most common spirochete causing Lyme disease. The natural host for *Borrelia* is the white-footed mouse and white-tailed deer.

Approximately 50% of patients recall a tick bite. About 3 to 32 days (median 7) after the bite, peripheral expansion of erythema with central clearing around the primary inoculation site ensues, resulting in lesions reaching 5cm in diameter or greater. Not all patients with tick bites will develop infection - ticks must be attached for at least 24 hours for transmission of *Borrelia* to occur. Futhermore, not all patients with clinical infection will develop erythema migrans, estimates range from 60-90% of patients. About 25% of patients will develop secondary lesions, either due to multiple tick bites or disseminated disease. Lesions tend to appear similar, but may be smaller and less pronounced. In general, the lesions are asymptomatic but pain and pruritus have been reported, particularly at the primary bite site. In the acute stage, influenza-like symptoms with headache, fatigue, arthralgias, myalgias, fever, conjunctivitis, lymphadenopathy and hepatitis can accompany the cutaneous manifestations.[2]

Clinical evidence of erythema migrans is the most sensitive and diagnostic evidence for early infection. Diagnosis can be confirmed via serologic testing, but is not required. Seroconversion typically occurs over a few weeks, therefore false negative results may occur in the acute stage. The Centers for Disease Control and Prevention advocates a two tiered serologic testing protocol, utilizing an enzyme linked immunoassay (EIA) followed by a confirmatory western blot. Antibodies typically persist for months or years following infection, and cannot always distinguish between acute and past infections. Repeat serologic testing for resolution of disease is not recommended. Skin biopsy typically demonstrates a gyrate erythema, and eosinophils and plasma cells may be present in the inflammatory infiltrate. A silver stain, such as the Warthin-Starry stain, can be used to demonstrate spirochetes.[3]

For adults and children greater than 8 years with early localized disease, oral doxycycline 100mg twice daily for 2-3 weeks is recommended. For those with early disseminated or mild chronic disease, a regimen lasting 2-4 weeks is recommended. In those allergic to doxycycline, pregnant woman or children less than 8 years, amoxicillin is the preferred alternative. Complications in untreated patients include arthritis (60%) within weeks to months, neurologic manifestations (10%) and cardiac complications (5%). Removal of ticks in less than 24 hours can generally prevent transmission of Lyme disease. Antimicrobial prophylaxis is recommended in adults from endemic areas within 72 hours of tick removal, for ticks attached for greater than 36 hours, with a single dose of 200mg of doxycycline.[3]

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PRESENTERS

Adaobi I. Nwaneshiudu, MD, PhD, Edidiong Kaminska, MD MBS, Arlene Ruiz de Luzuriaga, MD MPH, Maria Tsoukas MD, PhD, Diana Bolotin, MD, PhD

HISTORY OF PRESENT ILLNESS

A 54 year-old female with history of primary biliary cirrhosis status post liver transplantation in 1997, on oral tacrolimus for chronic immunosuppression, presented with new onset of a red rash, of unknown duration, on her trunk. She was hospitalized for fevers greater than 102^{o}F and chills, and was diagnosed with *Escherichia coli* bacteremia. Her hospital stay was complicated with volume overload and acute renal failure necessitating hemodialysis. The bacteremia was treated with cefepime intravenously but she continued to have fevers up to 100^{o}F and chills. The patient had been treated with vancomycin for presumed cellulitis on her trunk for one day prior to the dermatology consult, without improvement.

PAST MEDICAL HISTORY

Hypertension, primary biliary cirrhosis status post liver transplantation, recurrent cirrhosis complicated with esophageal bleeding, sicca syndrome, diabetes mellitus, atrial fibrillation, peptic ulcer disease, neuropathy, obesity.

FAMILY HISTORY

Non-contributory

MEDICATIONS

Amlodipine, calcium carbonate/vitamin D3, furosemide, ibandronate, lactulose, rifaximin, spironolactone, tacrolimus, ursodiol, zinc sulfate , gabapentin

ALLERGIES

Penicillin, cyclosporine

PHYSICAL EXAMINATION

There were multiple large, erythematous, edematous plaques on her buttocks, upper extremities, right back, and left flank. Scattered erythematous, edematous papules were noted on the upper back, chest and intertriginous areas. Diffuse pitting edema was noted on extremities and trunk, with one bulla on the mons pubis.

DERMATOPATHOLOGY

Histopathology revealed prominent papillary dermal edema with a mixed inflammatory cell infiltrate composed of abundant neutrophils intermixed with lymphocytes, histiocytes and eosinophils. Leukocytoclastic vasculitis was not noted.

LABORATORY DATA

Complete blood count: Leukocytes 4.1 K/μL (3.5-11.0), hemoglobin 8.1 g/dL (11.5-15.5), platelets 104 K/μL (150-450)
Chemistries: Creatinine 1.7 mg/dL (0.5-1.4)
Tissue cultures for bacteria and fungi were negative

DIAGNOSIS

Cellulitis-like Sweet's syndrome

TREATMENT AND COURSE

The lesions improved rapidly within 48 hours after initiation of treatment with 40mg of prednisone daily, with near resolution after nine days. Prednisone treatment was tapered slowly over 40 days. The patient has not followed up in dermatology clinic due to re-admissions for significant volume overload, and is currently on the kidney transplant list.

DISCUSSION

Acute febrile neutrophilic dermatosis, also known as Sweet's syndrome, was originally described by Dr. Robert Sweet in 1964.[1,2] Sweet's syndrome is postulated to be a hypersensitivity reaction to infection, autoimmune disease, inflammatory bowel disease or malignancy. Various infections including bacterial, viral, fungal, mycobacterial and protozoan have been associated with the onset of Sweet's syndrome, and this is thought to represent an altered immune response to the infectious organism. Of these infectious agents, *Streptococcus pneumoniae* is the most common.[3] Dysregulation of different cytokines, including IL-1, IL-3, IL-6, IL-8, and IFNγ has been identified in this disorder.[3] Histopathology of a lesional biopsy typically reveals marked edema of the papillary dermis, with an aseptic mixed inflammatory infiltrate predominantly consisting of mature neutrophils and leukocytoclasia without vasculitis.

Three different variants are commonly recognized, namely classical, malignancy-associated, and drug-induced. Classical Sweet's syndrome typically affects middle-aged women. Skin lesions tend to affect the head, neck and upper extremities and present as edematous, erythematous papules and plaques with a pseudovesicular appearance.[2] The diagnosis requires fulfillment of 2 major criteria: 1) abrupt onset of tender, erythematous edematous plaques and nodules and 2) typical histopathological features for Sweet's syndrome; and at least two of four minor criteria: 1) precedent respiratory or gastrointestinal infection, vaccination, inflammatory disease, malignancy or pregnancy; 2) presence of malaise and fever; 3) leukocytosis with left shift, elevated erythrocyte sedimentation rate or C-reactive protein levels; and 4) excellent response to systemic corticosteroids. [3]

Malignancy-associated Sweet's syndrome occurs in both hematologic and solid-organ cancers. The most common associated malignancy is acute myelogenous leukemia. This subtype has more widespread distribution, including involvement of the lower limbs, and may have atypical presentations mimicking facial/periorbital cellulits, or sporotrichoid nodules.[5] Lesions are frequently bullous, hemorrhagic and ulcerated and can bear close resemblance to pyoderma gangrenosum.[1,6] Drug induced Sweet's syndrome is rare but is more common in middle-aged women, with skin lesions usually appearing 5-7 days after first administration of the offending drug. The associated fever subsides 1-3 days after drug cessation and skin lesions clear in 3-30 days.[4] The distribution of cutaneous lesions favors legs, trunk and neck. The most common medications implicated are granulocyte colony-stimulating factor, minocycline, trimethoprim-sulfamethoxazole, antiepileptics, antihypertensives, oral contraceptives and retinoids.[4]

Sweet's syndrome may exhibit pathergy which can present as exacerbation of lesions at sites of IV catheters.[1] Sweet's syndrome is prone to misdiagnosis as cellulitis with patients being treated with systemic antibiotics without improvement. Rare variants of Sweet's syndrome have been described and include skin manifestations mimicking necrotizing fasciitis and cellulitis, including facial cellulitis. Necrotizing fasciitis-like Sweet's syndrome was reported in three patients who were septic and developed a localized, tender, indurated erythematous-violaceous plaque after therapy with granulocyte colony-stimulating factor.[7] Widespread "giant cellulitis-like" Sweet's syndrome, such as presented in this case, was previously described in three patients. All of the cases reported a presentation in obese patients with recurrent fever and widespread infiltrated plaques with bullous appearance. Histopathology revealed classic findings of Sweet's syndrome and two of the patients were found to have an underlying malignancy i.e. multiple myeloma or breast cancer. [1] Of note, no

malignancies have been identified in our patient to date.

The most effective therapy in Sweet's syndrome is oral prednisone, 0.5 to 1.0mg/kg/d with long taper over 4-6 weeks. Lesions typically show rapid response with marked improvement within 24-48 hours. Topical steroids and calcineurin inhibitors can be applied to localized lesions for symptomatic relief.[1]. In addition to corticosteroids, other systemic treatment options include colchicine, potassium iodide, indomethacin, cyclosporine or dapsone. Recurrences of Sweet's syndrome may occur regardless of treatment especially in malignancy associated Sweet's syndrome, and may herald recurrence of the malignancy.[3]

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PRESENTERS
Sonya Kenkare MD, Eduardo Moioli, MD, PhD, Christopher Shea, MD, Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS
72 y/o H male with h/o Stage IVb adenocarcinoma of the lung initiated Zelboraf (vemurafenib) chemotherapy on 9/20/13. He has previously received radiation therapy for treatment of this lesion. After 20 days of therapy he presented to dermatology clinic with a 1 week history of a pruritic rash on the torso and the proximal upper and lower extremities.

PAST MEDICAL HISTORY
B-RAF mutated non small cell adenocarcinoma of the lung, hypertension, hyperlipidemia

FAMILY HISTORY
No known family history of skin cancer

MEDICATIONS
Albuterol, atorvastatin, benzonatate, budesonide, dexamethasone, diphenhydramine, folic acid, hydrocodone, magnesium hydroxide, metoprolol, nystatin powder, ondansetron, prednisone, prochlorperazine, zelboraf

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Erythematous plaque approximately 25 cm in diameter on the central chest and back. Numerous perifollicular erythematous papules on the shoulder and the anterior thighs.

DERMATOPATHOLOGY
Dilated eccrine gland ducts surrounded by a moderate inflammatory infiltrate of lymphocytes and neutrophils in the upper dermis. Squamous metaplasia and dyskeratosis on the eccrine ductal epithelium are present.

LABORATORY DATA
None

DIAGNOSIS
Eccrine squamous syringometaplasia (ESS) on vemurafenib

TREATMENT AND COURSE
Vemurafenib therapy discontinued due to skin toxicity. Prednisone taper initiated. Vemurafenib was later re-initiated at 50% of the dose and the patient was able to tolerate the treatment without recurrence of ESS.

DISCUSSION
Vemurafenib is a BRAF inhibitor used to treat patients with BRAF mutations harboring the V600E mutation. The presence of the V600E mutation leads to a sustained activation of the mitogen-activated protein kinase (MAPK) pathway in the absence of any growth factor signal. Selective BRAF inhibitors like vemurafenib interrupt this proliferative pathway to yield significant, but transitional tumor reduction.

Several cutaneous adverse events have been described with the use of vemurafenib. Keratoacanthomas have been reported in 8% of patients and SCCs have been seen in 12% of patients. Eccrine squamous syringometaplasia is considered another squamoproliferative adverse event of vemurafenib. One case report demonstrated improvement of the eruption with decrease of the dose of vemurafenib.

Eccrine squamous syringometaplasia has been well described as a side effect of various drugs including cyclophosphamide, pegylated liposomal doxorubicin and hormonotherapy like tamoxifen. It is clinically characterized by a symmetric cutaneous eruption composed of papules and vesicles and is often found in intertriginous areas. Squamous metaplasia of eccrine ductal epithelium is seen on histopathology of the skin biopsy specimen..

The pathogenesis of ESS remains unknown. It may be related to a direct toxicity of the therapeutic agent on eccrine ducts secondary to a high concentration of the drug in sweat. Vemurafenib is also known to be responsible for a deregulatory effect on epidermal origin cells leading to lesions such as SCC. This squamoproliferative effect may be linked to a paradoxical activation of MAPK signaling. It is supposed that in the presence of a pre-existing RAS mutation in keratinocytes, vemurafenib would lead to a paradoxical up-regulation of wild-type BRAF, which potentiates the activity of the MAPK pathway, resulting in a sustained proliferative signal. Potentially, this might allow cells of the eccrine duct that have undergone squamous metaplasia the opportunity to proliferate.

Our case is an example of the rare but well-characterized condition of vemurafenib-induced eccrine squamous syringometaplasia.

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