Chicago Dermatological Society

December 2012
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Saturday, December 8, 2012

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.

8:00 a.m.	**Registration Opens** *DCAM Main Lobby (near the elevators)* Continental Breakfast Exhibitors (open throughout conference) *4th Floor South Atrium*
8:30 a.m. - 9:30 a.m.	**Resident Lecture** – *4th Floor North Atrium* "Practical Ways to Improve Patients' Treatment Outcomes" *Steven R. Feldman, MD, PhD*
9:00 a.m. - 10:30 a.m.	**Clinical Rounds** Patient & Poster Viewing *Dermatology Clinic 3A (DCAM - 3rd floor)* Slide Viewing *DCAM 1st Floor, Suite D, Room 1333*
10:45 a.m. - 11:45 p.m.	**General Session** - *4th Floor North Atrium* LORINCZ LECTURE: "Tanning: An Addictive Behavior" *Steven R. Feldman, MD, PhD*
11:45 p.m. - 12:30 p.m.	**Box Lunches & visit with exhibitors** *4th Floor South Atrium*
12:30 p.m. - 12:50 p.m.	**CDS Business Meeting** – *4th Floor North Atrium*
12:50 p.m. - 2:30 p.m.	**Case Discussions** – *4th Floor North Atrium*
2:30 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS monthly meeting will be the "President's Program" and Awards Luncheon: Wednesday, **February 13, 2013** at the Stephens Convention Center in Rosemont.

Also... the CDS Medicare/Coding Seminar – for doctors *and* office staff – will be on Saturday, **January 26, 2013** at the Stephens Convention Center in Rosemont. Meeting announcements will be sent out soon.

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

Guest Speaker

STEVEN R. FELDMAN, MD, PHD

Professor of Dermatology, Pathology & Public Health Sciences
Wake Forest Baptist Health
Winston-Salem, North Carolina

Delivering the Allan Lorincz Lecture

Steven R. Feldman, MD, PhD is Professor of Dermatology, Pathology & Public Health Sciences at Wake Forest University Health Sciences in Winston-Salem, North Carolina. Dr. Feldman comes to the CDS as a graduate of the University of Chicago (BA, 1980). He earned his medical degree and a PhD from Duke University Medical Center (1985). Residency training included psychiatry (1985) at Duke University; Medicine (1986-87), also at Duke; Dermatology (1987-90), North Carolina Memorial Hospital in Chapel Hill; and Dermatopathology (1990-91) at the Medical University of South Carolina in Charleston. Dr. Feldman is board certified in dermatology and with a special qualification in dermatopathology.

Dr. Feldman's major clinical interest is psoriasis, and his research studies focus on psoriasis and health service research in dermatology. He has published more than 100 peer reviewed articles and is a primary co-investigator in many research grant projects. Among many professional appointments and activities, Dr. Feldman is on the editorial board of the Journal of the AAD and for Skin & Aging..

Continuing Education Credit

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Conference"

December 8, 2012 *Chicago, IL*

Participants must attend entire session to receive full credit. Please complete the CME claim form included in your meeting materials and return to the COS registration table before you leave the conference. A certificate will be sent to you following the meeting. Also, we ask that you complete the evaluation form and return to the CLUB registration table. The information collected as part of this process represents an important part of the CME planning process.

The Colorado Foundation of Medical Care (CFMC) will retain a record of attendance on file for six years. CFMC contact information: 303-695-3300, ext. 3372

JOINT SPONSOR STATEMENT

This Continuing Educational activity is Joint-sponsored by the **Colorado Foundation for Medical Care, Office of Continuing Education** and the **Chicago Dermatological Society**. **CFMC is accredited by the ACCME to provide continuing medical education for physicians.**

GOAL/PURPOSE

To broaden the clinical knowledge of dermatologists with respect to diagnostic and therapeutic options.

SESSION OBJECTIVES

Upon completion of sessions, participants will be able to apply new knowledge and skills in the area of physician learning.

1. Describe factors that drive people's decision to tan
2. Discuss the evidence that tanning is an addictive phenomenon

.CREDIT STATEMENTS

CME CREDIT

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 joint sponsorship of the Colorado Foundation for Medical Care, Office of Continuing Education (CFMC OCE) and Chicago Dermatological Society. CFMC is accredited by the ACCME to provide continuing medical education for physicians.

The Colorado Foundation for Medical Care 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.

OTHER HEALTH CARE PROFESSIONALS

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 STATEMENTS

Steve Feldman, MD	Grant Research: Galderma Consultant: LEO

All other members of the faculty and planning team have nothing to disclose nor do they have any vested interests or affiliations. **It is the policy of the Chicago Dermatological Society and Colorado Foundation for Medical Care (CFMC) that the faculty discloses real or apparent conflicts of interest relating to the topics of the educational activity.**

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PRESENTERS
Sonya Kenkare MD, Carlos Paz, MD, PhD, Brian Pucevich, MD, Vesna Petronic-Rosic, MD, MSc, Maria Tsoukas, MD, PhD

HISTORY OF PRESENT ILLNESS
A 77-year-old man with a history of malignant mesothelioma presented with a three week history of rapidly growing flesh-colored plaques on the dorsal and ventral penile shaft. Two months prior to his initial dermatology consultation, the patient had been started on TGFβ antagonist therapy for malignant mesothelioma.

REVIEW OF SYSTEMS
The patient denied constitutional or genitourinary symptoms.

PAST MEDICAL HISTORY
Mesothelioma s/p chemotherapy, hypercholesterolemia, hypothyroidism, and gastrointestinal reflux disease

MEDICATIONS
Atorvastatin, levothyroxine, lansoprazole, GC1008 (TGFβ monoclonal antibody)

ALLERGIES
None

FAMILY/SOCIAL HISTORY
There is no family history of non-melanoma skin cancer. The patient is a retired construction worker. He is happily married and has two children.

PHYSICAL EXAMINATION
On physical examination, there was a 1.3 x 0.7 cm and 2.3 x 1.5 cm flesh-colored, pearly, verruciform plaque on the dorsal and ventral penile shaft, respectively

LABORATORY DATA
A complete blood cell count with differential, comprehensive metabolic panel, and fasting lipid panel were all within normal limits.

IMAGING STUDIES
CT Chest and Upper Abdomen: Left hemithorax with pleural thickening and volume loss compatible with known history of mesothelioma. Pleural tumor invades the pericardial fat and extends anterior. Multiple large pericardiophrenic lymph nodes are noted.

HISTOPATHOLOGY
Two 4-mm punch biopsy specimens from lesions on the dorsal and ventral penile shaft showed a proliferation of pink glassy keratinocytes with severe cytologic atypia and an increased number of mitotic figures. There is budding of the atypical keratinocytes from the epidermis into the dermis.

In situ hybridization for HPV (human papillomavirus) high-risk and low-risk groups were both negative.

DIAGNOSIS
TGFβ-induced squamous cell carcinoma

TREATMENT AND COURSE

Following the patient's biopsy-proven diagnosis of squamous cell carcinoma, the TGFβ chemotherapy was discontinued and the lesions on the ventral and dorsal penile shaft were excised with a 4mm margin. Despite complete excision and treatment with imiquimod cream, the patient developed new lesions adjacent to the initial excision sites and on the scrotum. These lesions were also excised and treatment with fluorouracil was initiated. Since completing TGFβ chemotherapy and receiving field treatment with fluorouracil, the genital lesions have resolved and he has not developed any new penile or scrotal growths. The patient is currently being followed by the Dermatology and Hematology/Oncology services at the University of Chicago.

DISCUSSION

Transforming growth factor β (TGFβ) is a multifunctional cytokine involved in the regulation of a wide variety of cellular processes including cell homeostasis and differentiation. TGFβ has also been shown to be involved in cancer development and progression and is associated with advanced disease and poor prognosis. TGFβ is overexpressed in a wide variety of tumors, including malignant mesothelioma, an aggressive and lethal pleural cancer. Recent evidence from murine studies indicates that inhibition of TGFβ effectively abrogates tumor growth in malignant mesothelioma and other cancers.

A variety of TGFβ antagonist agents, including monoclonal antibodies, antisensene oligonucleotides, and small-molecule inhibitors, have been developed for preclinical and clinical investigation. In a phase II clinical trial, the University of Chicago is currently investigating the overall safety and effectiveness of the anti-TGF monoclonal antibody, GC1008, in relapsed malignant pleural mesothelioma. The effectiveness of GC1008 in other cancers, such as melanoma and renal cell carcinoma, has already been investigated. In the latter study, GC1008 did not exhibit any dose limiting toxicity but did have the following side effects: rash (including 2 cases of eruptive keratoacanthomas), fatigue, headache, epistaxis, gingival bleeding and gastrointestinal symptoms.

Consistent with the side effects seen in the melanoma study, our patient developed invasive squamous cell carcinomas (SCCs) of the penis and scrotum. The mechanism behind the development of these tumors is unknown. The authors of a study showing that mice lacking TGFβ receptor signaling develop invasive SCCs in the anal and genital epithelia, and that TGFβ signaling is diminished in human genital SCCs postulated that anogenital skin loses the ability to maintain homeostasis between proliferation and apoptosis much faster than other skin. Thus, in the setting of TGFβ inhibition, the diminished capacity of aged anogenital skin to maintain homeostasis results in the development of SCCs. Additional studies are needed to determine whether this hypothesis might explain the eruption of SCCs on the penis and scrotum seen in our patient.

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PRESENTERS

Juliana Basko-Plluska, MD, Brian Pucevich, MD, Arlene Ruiz de Luzuriaga, MD, MPH, Bernhard Ortel, MD

HISTORY OF PRESENT ILLNESS

A 58-year-old female with a past medical history significant for spindle cell sarcoma of the right femur diagnosed in 2006, status post chemoradiation, partial resection and endoprosthetic reconstruction in 2008, presented with two weeks of expanding erythema and worsening pain of the right thigh. A month prior to presentation, the patient noted swelling of the right lower extremity. A right lower extremity Doppler was negative for deep venous thrombosis. Two weeks later, she developed erythema and increasing tenderness over the right lateral thigh, which prompted several visits to the Emergency Department. She was treated for presumed cellulitis with oral antibiotics without improvement. Subsequently, she was admitted and started on broad-spectrum IV antibiotics. The erythema and pain continued to worsen to the extent that the patient could hardly ambulate. CT of the right lower extremity showed no fluid collections, fractures or displacement of the hardware but was positive for markedly enlarged right inguinal and external iliac lymph nodes. Dermatology was consulted for further evaluation.

PAST MEDICAL HISTORY

Spindle cell sarcoma of the right femur- diagnosed in 2006, status post partial resection, chemoradiation and endoprosthetic reconstruction in 2008
Breast cancer- diagnosed 10 years ago, status post lumpectomy and radiation therapy
Pituitary adenoma- status post resection and gamma knife therapy
Major depression

REVIEW OF SYSTEMS/ FAMILY HISTORY/ SOCIAL HISTORY

Review of systems was notable for diaphoresis, decreased activity, pain and redness of the right lower extremity. Notably, the patient denied fever, chills, night sweats or weight loss.
Family and social history were non-contributory.

MEDICATIONS

Cefepime 2g IV Q8h, Vancomycin 1,500mg IV Q12h, Furosemide 40mg PO daily, Lexapro 20mg PO QHS, Hydrochlorothiazide 12.5mg PO daily, Zolpidem 5mg PO daily, Trazodone 100mg PO QHS PRN, Nexium 20mg PO BID, Clonazepam 1mg PO BID PRN

ALLERGIES

None

PHYSICAL EXAMINATION

A 12 x 6 cm, deep red to violaceous, indurated plaque with cobblestoning changes of the overlying skin was noted on the right lateral thigh, within a region of brawny, non-pitting edema. Several erosions with yellow crust were noted within the plaque, adjacent to an old surgical scar. There were no intact vesicles or bullae.

DERMATOPATHOLOGY

Two punch biopsy specimens were obtained from the right lateral thigh, one for regular histology and one for tissue culture. Pathology demonstrated a proliferation of spindle cells, focally forming anastomosing vascular structures, lined with pleomorphic, large and hyperchromatic endothelial cells. Anti-CD31 stained the entire spindle cell proliferation, emphasizing poorly-formed vascular structures. Anti-CD3 stained only tumor-infiltrating lymphocytes. Anti-CD20 labeling was negative. The gram stain, methenamine silver stain, periodic acid-Schiff stain and the Fite stain were all negative. Tissue culture

was negative for bacteria, acid fast bacilli and fungi.

LABORATORY DATA
Normal: complete blood count, comprehensive metabolic panel, blood cultures

IMAGING
CT right lower extremity: No loculated fluid collection is identified to suggest an abscess, although an early inflammatory process cannot be excluded. Markedly enlarged right inguinal and external iliac lymph nodes are present, which may be reactive or from an infiltrative process.
PET Scan: Extensive markedly hypermetabolic tumor involving the right thigh and widely metastatic to numerous lymph nodes in the neck, chest, abdomen and pelvis.

DIAGNOSIS
Angiosarcoma in the setting of chronic lymphedema

TREATMENT AND COURSE
Given metastatic disease and severe pain, palliative chemotherapy was discussed with the patient and her family. The patient received the first dose of paclitaxel at 80 mg/m^2 during her hospital stay at the University of Chicago, with the plan to receive the rest of chemotherapy cycles by her local oncologist. In addition, she received Fentanyl patch, Methadone PO and Hydromorphone PCA to help control the pain. Patient was discharged home after adequate pain control. Family is currently seeking additional care at MD Anderson Cancer Center and pursuing genetic testing given the occurrence of three different tumors.

DISCUSSION
Angiosarcoma is a rare, aggressive malignant vascular tumor, which accounts for less than 1% of all soft tissue sarcomas. The most common form of angiosarcoma is cutaneous angiosarcoma on the scalp or face of an elderly male. Although most angiosarcomas are sporadic, predisposing conditions include chronic lymphedema, radiation, exposure to toxins (eg, vinyl chloride) and foreign bodies.
Angiosarcomas that arise in the setting of chronic lymphedema present as firm, coalescing violaceous nodules or an indurated plaque on a background of brawny, non-pitting edema. Post-irradiation angiosarcomas appear as infiltrative plaques or nodules in or near the area of tissue irradiated. Both types of angiosarcomas typically present several years post therapy and are associated with a worse prognosis. Metastasis to regional lymph nodes and lung are common.

Angiosarcomas are clonal proliferations of malignant cells expressing endothelial differentiation. Approximately 50% of cases express markers of lymphatic differentiation. Cutaneous angiosarcomas exhibit a range of pathologic morphology and differentiation. Immunohistochemistry is often necessary to confirm the diagnosis. CD31 is the single best marker with high sensitivity and specificity. CD34 and factor VIII are also expressed in most angiosarcomas, but less frequently in poorly-differentiated tumors.

A significant proportion of angiosarcomas arise in the setting of chronic lymphedema after a 4- to 27-year latency. This is known as Stewart-Treves syndrome (STS). Although classically described as a consequence of radical mastectomy, angiosarcoma has been documented to occur in cases of congenital and with chronic secondary lymphedema, suggesting that chronic lymph stasis predisposes to the onset of angiosarcoma. STS has also been observed in the lower extremity, albeit rarely, and can result from congenital, idiopathic, traumatic, filarial or post-surgical causes of lymphedema. The pathophysiology of STS is a matter of controversy. Stewart and Treves speculated that a systemic carcinogenic factor was the causative agent given findings of a high incidence of a third malignancy in patients with post-mastectomy angiosarcoma. This hypothetical factor has yet to be isolated. There is now evidence that chronic lymphedema impairs local immune surveillance by disrupting trafficking of the immunocompetent cells

in the lymphedematous areas, thus making the lymphedematous area an immunologically vulnerable area predisposed to malignancy.

Rare, post-irradiation angiosarcomas have been documented, usually as abdominal or chest wall tumors following radiation for gynecologic malignancies or breast carcinoma. Recently, with increased use of breast-sparing surgery paired with irradiation for breast carcinoma, more post-irradiation sarcomas have arisen in breast parenchyma and overlying skin, with an average post-treatment delay of 6 years.

The overall prognosis of angiosarcoma is extremely poor, with a median survival time of 15-30 months. Stewart-Treves syndrome is associated with an even worse prognosis. Treatment should consist of radical, wide surgical excision and subsequent radiotherapy. However, even with negative margins by histologic examination, the recurrence rate and chance of metastatic disease is high due to the tendency of this tumor for multifocality. Aggressive local therapy with amputation with or without radiation therapy seems to offer the best outcomes for patients with localized disease. Chemotherapy is employed for palliation of patients with metastatic or incurable disease.

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PRESENTERS
Edidiong Celestine Ntuen Kaminska, MD, MBS, Vesna Petronic-Rosic, MD, MSc, Keyoumars Soltani, MD

UKNOWN CASE

PRESENTERS
Adena E. Rosenblatt, MD, PhD, Erica R. Aronson, MD, Vesna Petronic-Rosic, MD, MSc, Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
An 11 month old boy with biliary cirrhosis and end stage liver disease of unknown etiology presented to dermatology with dark lesions over his arms and legs. According to his parents, the plaques had developed over the course of the 2 -3 months prior to presentation. Topical hydrocortisone 1% ointment helped slightly with lightening of the color but did not smooth the lesions out or help to resolve them. The lesions are not itchy or painful and do not bother the patient.

PAST MEDICAL HISTORY
At 5 months of age, the patient was admitted to Children's Hospital of Wisconsin for failure to thrive, jaundice, ascites, and hypotonia. Liver biopsy revealed cirrhosis, likely secondary to an inborn error of bile metabolism of unknown etiology. In addition, the patient was found to have Fanconi syndrome, Ricketts, and fat soluble vitamin deficiencies, for which he is on high calorie G tube feeds and vitamin supplementation, as well as cornstarch.

FAMILY HISTORY
No family history of liver disease, genetic, neurological, or cutaneous illnesses.

MEDICATIONS
Calcitriol 0.5 mcg BID, Vitamin K 2.5 mg daily, Spironolactone 40 mg PO BID, Vitamin E 800 Units Daily, Lansoprazole 7.5mg/2.5ml BID, Ergocalciferol 40,000 Units daily, Valsartan 80 mg PO BID.

ALLERGIES
No Known Drug Allergies

PHYSICAL EXAMINATION
11 month old male with scleral icterus, enlarged abdomen with G tube in place as well as generalized jaundice. Over extensor knees onto inner thighs, extensor elbows onto upper arms and on dorsal hands and feet there are well-demarcated hyperpigmented, hyperkeratotic plaques with violaceous border. Some of the plaques have overlying scale.

DERMATOPATHOLOGY
The epidermis is papillomatous and with hyperkeratosis. There is an increased amount of pigment in the basal layer.

LABORATORY DATA
Glucose 66 mg/dL (60-109), Sodium 127 mEq/L (134-149), Potassium 4.8 mEq/L (3.5-5.0), Chloride 98 mEq/L (95-108), Carbon Dioxide 20 mEq/L (23-30), BUN 8 mg/dL (7-20), Creatinine 0.2 mg/dL (0.5-1.4), Calcium 7.9 mg/dL (8.4-10.2)
Total protein 5.1 g/dL (nl 6-8.3), Albumin 2.3 g/dL (nl 3.5-5.0)
Total Bilirubin 19.8 mg/dL (0.1-1.0), Conjugated Bilirubin 14.4 mg/dL (0.0-0.3), Unconjugated Bilirubin 5.4mg/dL (0.1-1.0)
Alk Phos 406 U/L (nl 100-390), AST 177 U/L (nl 8-37), ALT 176 U/L (nl 8-35), GGT 52 U/L (nl 11-63)
Serum Alpha fetoprotein 41938 ng/ml (<9)
Complete blood count: Leukocytes 10.4 K/µL (6.0-17.3), hemoglobin 8.2 g/dL (10.3-13.2), platelets 211 K/µL (150-450)
Differential: Neutrophils 59%, lymphocytes 24%, monocytes 14%, eosinophils 2%, basophils 1%
Hepatitis panel- Nonreactive

DIAGNOSIS

Generalized Acanthosis Nigricans in the setting of cryptogenic liver failure with resolution after successful liver transplantation

TREATMENT AND COURSE

The patient received a cadaveric liver transplant at 12mo of age, which was complicated by inability to establish arterial flow to graft and hepatic artery thrombosis. Two days after receiving his first transplant he was re-transplanted successfully. A month following his transplant, the skin lesions had resolved.

DISCUSSION

Acanthosis Nigricans is typically a symmetric eruption consisting of velvety, hyperpigmented, sometimes papillomatous, cutaneous thickening that can occur on any part of the body but characteristically affects the axillae, nape of the neck, groin, and antecubital fossae. These lesions are usually asymptomatic. Pathology typically demonstrates hyperkeratosis and epidermal papillomatosis.

Acanthosis nigricans is most commonly associated with insulin resistant states including diabetes mellitus, but is also seen in more rare syndromes in which insulin resistance is a feature such as HAIR-AN syndrome and Rabson-Mendenhall syndrome. In addition, acanthosis nigricans is observed as a paraneoplastic phenomenon associated with malignancies such as adenocarcinoma of the gastrointestinal tract. Acanthosis nigricans has been associated with medications such as systemic steroids, nicotinic acid, diethylstilbestrol, and insulin. Acanthosis nigricans is observed in fibroblast growth factor receptor defect syndromes such as Beare-Stevenson cutis gyrate syndrome, Crouzon syndrome, and severe achondroplasia with developmental delay and AN (SADDAN syndrome).

The pathogenesis of acanthosis nigricans has not been completely elucidated but it is thought to be due to activation of epidermal growth factor receptor (EGFR), insulin-like growth factor receptor (IGFR1) and fibroblast growth factor receptor (FGFR), all of which are tyrosine kinase receptors. These receptors have potent mitogenic and anti-apoptotic effects on keratinocytes. The role of growth factors in the pathogenesis of acanthosis nigricans may explain its association with insulin resistance and malignancy. There is commonly an overexpression of growth factors in malignancy leading to an activation of the corresponding receptors. In insulin resistant states, the patient is usually hyperinsulinemic. The excess insulin binds to and activates IGFR1, due to its similarity in structure to the insulin receptor.

There is not an established relationship between cirrhosis, particularly biliary cirrhosis, and acanthosis nigricans. There is a case report from 1996 of a 58yo Caucasian male with primary biliary cirrhosis who presented with acanthosis nigricans that resolved after liver transplantation, similar to our patient. There is also a case report from 1951 of a patient with cirrhosis and acanthosis nigricans. The pathophysiology of acanthosis nigricans in cirrhosis is not known. Most likely it is related to growth factor regulation. Insulin resistance is commonly associated with chronic liver disease and may be the mechanism for acanthosis nigricans in our patient, despite a normal blood glucose. Upon liver transplantation the associated insulin resistance likely resolved, and we propose that without this stimulus of IGFR1, the acanthosis nigricans regressed.

Another consideration in the differential diagnosis for this patient was progressive and symmetric erythrokeratoderma. This is an inherited autosomal dominant condition that is thought to be due to a mutation in the loricrin gene. It is characterized by nonmigratory, hyperpigmented, symmetric plaques that are usually distributed on the extremities, buttocks and sometimes face. These lesions can sometimes spontaneously resolve during puberty. Pathology can be similar to acanthosis nigricans showing hyperkeratosis, irregular acanthosis, and variable papillomatosis. There have been no reported associations between progressive and symmetric erythokeratoderma and cirrhosis.

Given the clinical presentation, histopathology, and past medical history, we believe our patient had acanthosis nigricans that resolved after liver transplantation. We propose that the underlying mechanism involves regulation of growth factor and insulin signaling pathways.

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PRESENTERS
Monique Kamaria, MD, Christopher R. Shea, MD, Vesna Petronic-Rosic, MD, MSc, Bernhard Ortel, MD, Diana Bolotin, MD, PhD

HISTORY OF PRESENT ILLNESS
A 93 year old Caucasian female with a 12 year history of erythrodermic and plaque psoriasis, right lower extremity cellulitis and non-melanoma skin cancer presented for evaluation of regrowth of a keratotic nodule within the scar of a prior excision of a squamous cell carcinoma on her right shin as well as development of multiple dome-shaped nodules in the same area over several weeks. The lesions were increasing in size and number and were tender. Two weeks prior to the development of these growths, the patient was diagnosed with right lower extremity cellulitis requiring treatment with IV vancomycin. Up until the development of the lesions on her right lower extremitiy, her psoriasis was well controlled with topical steroids and emollients only. However, at the time of her visit and subsequent visits, her psoriasis had gradually progressed to involve a majority of her body surface area, with diffuse erythema and scaling. The patient's extensive psoriasis had been previously treated with a number of therapies, including topical steroids, tazorac, methotrexate, soriatane, narrow band UVB phototherapy, PUVA, and Enbrel. All therapies had yielded a partial response or had to be discontinued secondary to intolerance.

PAST MEDICAL HISTORY
Hypertension, emphysema, psoriasis, right lower extremity cellulitis, breast cancer, cutaneous squamous cell carcinoma, chronic kidney disease, hypercholesterolemia, osteoporosis

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
Former smoker - 5 pack year history

MEDICATIONS
Albuterol, Alendronate, Aspirin, Budesonide-formoterol, Lipitor, Calcium carbonate and Vitamin D, Combivent, Diltiazem, Miralax, Tiotropium inhaler (Spiriva®), Tolterodine-LA (Detrol LA®), Valsartan Mometasone ointment, Tacrolimus ointment

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
On physical exam, the bilateral lower extremities were diffusely erythematous with coarse yellow scale. A 1.5cm keratotic nodule with central hemorrhagic crust was noted within a linear scar on the right shin. Eight smaller (5-10 mm) dome shaped nodules with central keratotic crust were scattered on the medial and lateral right shin.

Additionally, the patient had diffuse erythema with fine exfoliative scale present on the face, trunk, and extremities. This was particularly prominent on the face, with well-demarcated erythematous psoriasiform plaques with confluent involvement of the central face and abrupt cessation at the neckline.

DERMATOPATHOLOGY
Biopsies of the large central nodule as well as two of the smaller lesions revealed keratinocytes with full thickness severe cytologic atypia extending from the epidermis into the dermis consistent with invasive squamous cell carcinomas (SCCs).

LABORATORY DATA

Normal: Complete blood count with differential

Comprehensive metabolic panel: Glucose 87 mg/dL (60-109), sodium 134 mEq/L (134-149), potassium 4.9 (3.5-5.0), chloride 98 mEq/L (95-108), carbon dioxide 25 (23-30), BUN 31 mg/dL (7-20), creatinine 1.3 mg/dL (0.5-1.4), **GFR 38 mL/min/BSA** (> 59)

DIAGNOSIS

Treatment of eruptive squamous cell carcinomas in the setting of psoriasis

TREATMENT AND COURSE

To be discussed

PRESENTERS
Mara Beveridge, MD, Monique Kamaria, MD, Vesna Petronic-Rosic, MD, MSc, Christopher R. Shea, MD

HISTORY OF PRESENT ILLNESS
A 25-year-old Latino woman underwent mesotherapy cellulite reduction injections on the hips and abdomen in Brazil and subsequently developed painful, suppurative abscesses at the injection sites. She reported a previous culture done in Brazil that was positive for a mycobacterium and was treated inconsistently in her home country with doxycycline, rifampin, metronidazole, and rifamate, but never completed a full course. After months of unresolving symptoms she presented to our clinic.

PAST MEDICAL/SURGICAL HISTORY
Non-contributory

REVIEW OF SYSTEMS
Patient denied night sweats, cough, shortness of breath, fever.

MEDICATIONS
None

ALLERGIES
No known drug allergies

FAMILY HISTORY
Non-contributory

SOCIAL HISTORY
International student at the University of Chicago for a study abroad program.

PHYSICAL EXAMINATION
One-to-five-centimeter, erythematous, painful, firm/indurated subcutaneous plaques and nodules were present on thighs and lower abdomen. Patient was afebrile and had normal vital signs.

LABORATORY DATA
Gram stain and bacterial culture were negative. Fungal smear and culture were negative. Acid-fast bacilli (AFB) smear was negative. AFB culture grew *Mycobacterium chelonae-abscessus* complex. Rapid-grower sensitivity studies showed it was susceptible to clarithromycin and amikacin; had intermediate susceptibility to cefoxitin and imipenem; and was resistant to ciprofloxacin, moxifloxacin, tobramycin, doxycycline, trimethoprim/sulfamethoxazole, and linezolid.

DERMATOPATHOLOGY
Punch biopsy from thigh: Focal spongiosis is present. There is a dense, granulomatous and mixed inflammatory cell infiltrate within the mid-dermis extending into the subcutaneous tissue. The periodic acid-Schiff stain is negative for fungi or significant basement membrane thickening. The methenamine silver stain is negative for fungi. The Gram stain is negative for bacteria. The Fite stain identifies rare Fite-positive elements consistent with mycobacteria. The Ziehl-Nielsen stain is negative for mycobacteria.

DIAGNOSIS
Mycobacterium chelonae-abscessus complex infection after mesotherapy injections

TREATMENT AND COURSE

Due to the resistance of the isolate the patient was referred to the Infectious Disease service. A PICC line was placed and she was treated with dual antibiotic therapy for the first month with tigecycline 50 mg IV BID and clarithromycin 500 mg PO BID. After one month her subcutaneous nodules had resolved, so tigecycline IV was discontinued and she was continued on oral clarithromycin for another two months to complete a three-month course. She has now returned to South America.

DISCUSSION

Non-tuberculous mycobacterial infections of the skin are rare but the incidence has been increasing in recent years. While there are few comprehensive data about prevalence in the United States, one large-scale retrospective study in Oregon reported a prevalence of 0.9 cases per 100,000 persons. The most common strains of non-tuberculous mycobacteria that cause cutaneous infections in humans are *Mycobacterium abscessus, M. fortuitum, M. chelonae, and M. avium.* The first cases were reported among immunosuppressed patients, particularly renal transplant patients. However, an increasing number of cases are being reported in immunocompetent individuals, especially in those undergoing invasive cutaneous procedures such as subcutaneous injections, acupuncture, tattoos, and mesotherapy.

Mesotherapy involves the injection of compounds into the subcutaneous space in an attempt to decrease the amount of adipose tissue. The solutions containing these compounds are frequently referred to as "cocktails;" commonly used active ingredients include phosphatidylcholine/deoxycholic acid, caffeine, and Conjonctyl®. Many of these compounds are marketed as homeopathic substances that do not require FDA approval and are manufactured in multi-use vials, leading to concern about the standardization and safety of these practices. Outbreaks occur when contamination happens at some point in the manufacturing, storage, or procedural stages. A recent outbreak of *M. chelonae* infections associated with four particular brands of tattoo ink in New York, Washington, Iowa, and Colorado demonstrated the enormity of the task required to identify, control, and recall the source of the infection.

Once an atypical mycobacterial infection has occurred, an accurate and timely diagnosis must be made. Diagnoses have traditionally been based on tissue cultures and swabs and this remains the general standard today. Even with rapid-growing strains, cultures can still take several days and the sensitivity is relatively low (80-85%). Staining is technician-dependent and can have false negatives, as seen in the case in which the Fite stain was positive but Ziehl-Nielsen was negative. An alternative method is PCR-restriction enzyme analysis which detects the 16S-23S rRNA gene internal transcribed spacer. Sensitivity and specifity of PCR are 0.5%-100% and 73%-100% respectively; the high variability is based on bacterial load. Proposed limitations of PCR include: degradation of DNA in archival materials, difficulties in extracting mycobacterial DNA, and decreased amplification as a result of formalin fixation.

While there is currently no standard guideline for the treatment of cutaneous *M. abscessus* infections there is general agreement that treatment regimens should involve more than one antibiotic and should be lengthy, in order to avoid antibiotic resistance such as occurred in this case. Most reported regimens include clarithromycin plus a fluoroquinolone or an aminoglycoside. A prospective, non-randomized observational study by Choi et al. of 52 patients infected with cutaneous *M. abscessus* after acupuncture compared clarithromycin plus amikacin to clarithromycin plus moxifloxacin. The latter group had a better clinical response; both groups had approximately equivalent side-effect profiles. Treatment time is typically determined by resolution of the lesions and often lasts 17-20 weeks.

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PRESENTERS

Adaobi I. Nwaneshiudu, MD, PhD, Edidiong Celestine Ntuen Kaminska, MD, MBS, Vesna Petronic-Rosic, MD, MSc

HISTORY OF PRESENT ILLNESS

A 63-year-old male with a history of signet-ring cell carcinoma (SRCC) of the esophagus presented with a 2-month history of painful growths on his trunk. The esophageal cancer had been treated with neoadjuvant chemotherapy (cisplatin and 5-fluorouracil), radiation, and esophagectomy 10 months prior to presentation.

PAST MEDICAL HISTORY

Signet-ring cell carcinoma of the esophagus, coronary artery disease, hypertension, glaucoma, gastroesophageal reflux disease

REVIEW OF SYSTEMS / FAMILY HISTORY / SOCIAL HISTORY

ROS/ Family history: Not contributory, Social history: Married, former smoker

MEDICATIONS

Aspirin 81mg daily, clopidogrel 75mg daily, ezetimibe 10mg daily, gabapentin 300mg three times a day, ramipril 5mg daily, metoprolol 25mg daily

PHYSICAL EXAMINATION

A tender, firm, erythematous, nodule was present on the left posterior shoulder. In addition, there was an erythematous nodule with central eschar in a surgical scar on the right lateral trunk that was firmly adherent to the underlying bony structures of the chest wall.

DERMATOPATHOLOGY

Histopathological assessment revealed numerous glandular structures within the dermis with focal signet ring differentiation coursing amongst the collagen bundles. Many atypical cells and mitotic figures were also noted.

LABORATORY DATA

Human epidermal growth factor receptor 2 (Her 2) expression: low level on immunohistochemistry
Serum carcinoembryonic antigen (CEA): **7.2** (0-3.4ng/mL)

DIAGNOSIS

Cutaneous metastasis of a poorly-differentiated esophageal signet-ring cell carcinoma

TREATMENT AND COURSE

The patient underwent further chemotherapy treatment with carboplatin.

DISCUSSION

Signet-ring cell carcinoma (SRCC) is a unique subtype of mucin-producing adenocarcinoma characterized by signet ring cell differentiation, i.e. abundant intracellular mucin accumulation within a single vacuole or microcyst, resulting in a compressed nucleus displaced toward the edge of the cell. Some authors have suggested that the signet ring cell is an intermediate form with features of both squamous and adenocarcinoma cells. Signet-ring cell carcinoma may arise in various organs including the esophagus, stomach, colon, urinary bladder, prostate, and breast. In addition, other tumors can demonstrate signet-ring cell differentiation including melanoma, primary cutaneous non melanoma skin cancers, lymphoma, and various adenocarcinomas.

Esophageal signet ring cell carcinoma is a rare, highly aggressive, histological variant of esophageal adenocarcinoma, with a dismal prognosis. The reported incidence ranges from 0.1-0.6%. Cutaneous metastasis is very rare. Histopathological evaluation typically reveals a mixture of glandular cells with signet ring differentiation and squamous cells, referred to as mucoepidermoid carcinoma. Assessing cytokeratin expression on immunohistochemistry may aid in determining the etiology of metastatic SRCC. Gastrointestinal signet ring cell carcinomas tend to be CK20 and CK7 positive, as shown in one series, while breast signet ring malignancies are negative for CK20 but positive for the estrogen receptor (ER). Esophageal IHC profile, in particular, is positive for CK20, CK7, AE1/AE3, and EMA. In cutaneous metastasis, these neoplastic cells have shown membrane expression of c-erb-B2, CD44v6, HER 2/neu and E-cadherin, which may facilitate the distant localization and survival, and is associated with disease progression and poor response to a cytotoxic regimen.

Esophageal SRCC is a highly fatal disease, and cutaneous metastasis portends an even worse prognosis, with most patients dying within 3 months. In one report, all of the patients in the study died within 2 years after the esophagectomy irrespective of whether they received chemotherapy or radiotherapy. In another series, most of the patients died of either local recurrence or widespread metastasis after treatment, with the overall 5-year survival rate being 24.4% in the total 25 cases, and 27.7% in the 22 resected cases. Locoregional disease is fatal because it leads to inanition (exhaustion from lack of nutrition) and aspiration. Poor prognosis is attributed to the diffusely infiltrating nature of the neoplasm, leading to widespread metastases before being clinically apparent Chemotherapy, radiation, and surgery are frequently employed for treatment. Patients with esophageal or EGJ adenocarcinoma who have signet ring cell or mucinous histology benefit substantially from preoperative chemoradiation and esophagectomy compared to surgery alone.

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PRESENTERS
Erica R. Aronson, MD, Edidiong Celestine Ntuen Kaminska, MD, MBS, Tunisia Finch, MD, Vesna Petronic-Rosic, MD, MSc, John Anastasi, MD, Maria Tsoukas, MD, Sarah L. Stein, MD

UKNOWN CASE

PRESENTERS
Sogyong Auh, MD, PhD, Vesna Petronic-Rosic, MD, MSc, Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
The patient is a 5 year old male who presents for evaluation of warts. He has a history of acute lymphoblastic leukemia, initially diagnosed two years prior to presentation to the dermatology clinic. At presentation, the patient was on maintenance chemotherapy with vincristine, methotrexate, and 6-mercaptopurine, and had developed warts on his feet over the prior 4 months. The patient's mother had been applying over the counter wart removers containing salicylic acid daily without improvement. She noted that the child was in pain as a result of the warts and was not able to participate in activities such as running.

PAST MEDICAL HISTORY
Acute lymphoblastic leukemia

FAMILY HISTORY
Noncontributory

MEDICATIONS
Methotrexate, 6-mercaptopurine, vincristine, Decadron, Bactrim

ALLERGIES
PEG-asparaginase, intravenous immunoglobulin

PHYSICAL EXAMINATION
This is a well-appearing, well-developed 5-year-old in no distress. Within the nail bed of the right distal great toe, there is a large verrucous exophytic plaque which is deforming the overlying nail plate. Involving the plantar aspect of the right great toe and the balls of both feet, there are numerous verrucous plaques and raised verrucous papules and nodules. There are no verrucous lesions on the hands or elsewhere on the body.

DERMATOPATHOLOGY
Right toe nail and nail bed: The epidermis has acanthosis and papillomatosis, without significant atypia. The granular layer is prominent. Dermal blood vessels are dilated. The GMS stain is negative for fungi.

LABORATORY DATA
Complete blood count: Leukocytes 1.9 K/µL (4.0-13.8), all other values within normal limits.
Differential: Neutrophils 65%, lymphocytes 21%, monocytes 10%, eosinophils 3%
Comprehensive Metabolic Panel: ALT 65 U/L (8-35), all other values within normal limits.

DIAGNOSIS
Verruca plantaris, extensive, in an immunocompromised patient on chemotherapy

TREATMENT AND COURSE
Initial treatment included Wart Peel®, a compounded topical preparation of 5-fluorouracil and salicylic acid, but the patient developed significant pain with the application of the medicine so it was discontinued. An intradermal test dose of Candida antigen did not elicit any response, therefore intralesional Candida injections were not pursued. The size and the location of the warts were causing significant disability, therefore the patient underwent surgical debulking of the largest lesions under anesthesia. Afterwards, the family applied topical 3% cidofovir to the sites of debulked warts daily and Veregen® (sinecatechins) ointment to all other warts daily. 5-Fluorouracil 5% cream under occlusion was

also used to treat regrowing lesions. Intermittent cryotherapy sessions were performed when the patient was sedated for bone marrow biopsies.

Initially, there was significant improvement in the patient's quality of life. However, despite several months of topical treatment, the warts recurred and again caused significant difficulty with walking and running due to pain in the feet.

Because of the significant negative impact of these warts on the patient's activities of daily living, after careful consideration the family elected a trial of intravenous cidofovir. Cidofovir was administered in consultation with hematology/oncology at a dose of 5 mg/kg weekly for 2 weeks, then every 2 weeks for a total of 5 cycles. Oral probenecid was administered pre and post infusion in conjunction with intravenous hydration with normal saline as is standard with IV cidofovir. The patient tolerated the treatments well.

Four months later, the patient had significant clearance of the plantar warts. Clearance coincided with cessation of chemotherapy, which happened about 1 month prior to wart resolution. Of note, the patient's blood counts did not normalize until about 10 months after stopping chemotherapy.

DISCUSSION

The human papillomavirus (HPV) is a non-enveloped, double-stranded DNA virus that infects skin and mucosal surfaces. Most treatments for HPV infection have no specific antiviral effect and are based on destruction of involved tissue. However, the viral DNA can persist in clinically normal skin, making it difficult to eliminate the virus. Patients with impaired cell-mediated immunity, such as patients with HIV infection and organ transplant patients receiving chronic immunosuppressive treatment, tend to be more difficult to treat as lesions are more numerous and more refractory to therapy.

Cidofovir is a nucleoside analog of deoxycytidine monophosphate that has antiviral activity against a broad range of DNA viruses. It inactivates viral DNA polymerase, halts DNA synthesis and induces apoptosis in HPV infected keratinocytes. It is approved by the Food and Drug Administration for treating resistant cytomegalovirus retinitis in patients with HIV. Potential side effects of intravenous cidofovir include nephrotoxicity, secondary to proximal tubular cell injury. This can be reduced by premedicating with probenecid and normal saline. Uveitis/iritis and neutropenia are less common side effects.

There are several case reports in the literature describing successful treatment of extensive warts with systemic cidofovir. Intravenous cidofovir has been successful in treating resistant HIV-associated verruca vulgaris in a patient with persistent severe immunosuppression. The patient was treated with a dose of 375 mg every 2 weeks with standard pretreatment with probenecid and intravenous hydration. After 7 cycles and surgical debulking of the largest verruca, the patient had clearance of lesions. Another case report described successful treatment of HPV infection in an immunosuppressed patient with HIV infection after 5 cycles. IV cidofovir has also been used in the context of immunosuppression secondary to myelodysplastic syndrome (MDS). In this case HPV 27 was identified by polymerase chain reaction. The patient was treated with IV cidofovir at a dose of 3.5 mg/kg (375 mg) once a week for 2 weeks then every two weeks for 18 weeks. However, more recently there has been a report of failure of IV cidofovir in treatment of generalized verrucosis in a patient with severe combined immunodeficiency. This patient was shown to have low-risk HPV type 57 in several cutaneous warts and high-risk HPV type 33 in a penile lesion. He was treated at a dose of 5 mg/kg for 2 weeks, followed by every other week for 3 months and did not show any clinical improvement in lesions. In this treatment resistant case, the HPV was a less common type, suggesting that response to cidofovir may be dependent on the specific HPV type.

Successful treatment of extensive warts in immunocompetent patients has also been described. The first

described pediatric case involved a patient with a history of congenital lymphedema, who had florid cutaneous warts on the bilateral hands, feet, and chin. The patient was treated with IV cidofovir at a dose of 5 mg/kg weekly for 2 weeks then every 2 weeks for a total of 5 cycles. Resolution of >90% of the lesions was observed 6 months after the last treatment.

In regards to our patient, it is unclear if treatment with 5 cycles of IV cidofovir, or reversal of immunosuppression led to clearance of the lesions. However, since the patient's blood counts did not fully normalize until almost a year after stopping chemotherapy, the reversal of immunosuppression was likely not complete when significant clearance of the warts was achieved.

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PRESENTERS
Min Deng, MD, Vesna Petronic-Rosic, MD, MSc, Maria M. Tsoukas, MD, PhD

HISTORY OF PRESENT ILLNESS
A 73-year-old female with a history of recurrent multiple myeloma presented with a pruritic, tender rash of 4 months duration. The rash was present on the distal anterior-lateral right lower extremity, as erythematous–purple, relatively soft confluent papules, plaques and nodules. Previous treatments included hydrocortisone cream and compression stockings, with no improvement.

PAST MEDICAL HISTORY
Multiple myeloma, IgG/lambda type
Chronic renal insufficiency, stage 4
Deep vein thrombosis (left common femoral vein)
Chronic lower extremity edema
Hypertension
Osteoarthritis

FAMILY HISTORY
Breast cancer
Diabetes mellitus type 2

MEDICATIONS
Lenalidomide 15mg qday, Dexamethasone 20mg qweek, Zoledronic acid q3 months, Multivitamin 1 tab qday, Aspirin 325mg qday, Calcium and Vitamin D qday, Hydrocodone-acetaminophen PRN pain, Hydrocortisone 1% cream BID, Lisinopril-Hydrochlorothiazide 20-12.5mg qday, Potassium chloride 40 mEq ER qday

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Confluent, relatively soft, tender, erythematous-purple papules, plaques and nodules with a smooth shiny surface distributed on the anterior and lateral distal right lower extremity. There was pitting edema of bilateral lower extremities.

DERMATOPATHOLOGY
Histopathological assessment revealed mild acanthosis of the epidermis. A dense, sheet like infiltrate of large, atypical plasma cells extended from the superficial dermis to the subcutaneous fat with grenz zone present. Multiple mitotic figures were present within the neoplasm. CD138 was strongly and diffusely positive in the neoplastic cells, but PAX5 was negative.

LABORATORY DATA
Serum Electrophoresis:

IgG - 1781 mg/dL (800-1700)
IgA – 13 mg/dL (100-490)
IgM – 6 mg/dL (60-370)
Kappa free light chain - 0.7300 mg/dL (0.3300-1.94)
Lambda free light chain - 333 mg/dL (0.5700-2.63)
Kappa/lambda ratio – 0.0022 (0.2600-1.65)

Skeletal survey: lucent lesions were seen throughout the axial skeleton, femur, humerus and radius. No myelomatous deposits were apparent in the right or left tibia/fibula.

DIAGNOSIS
Metastatic cutaneous multiple myeloma

TREATMENT AND COURSE
The patient completed palliative radiation of the right leg and foot (20Gy in 2Gy fractions over 2 weeks), with a decrease in the size of her lesions and significant improvement with her discomfort. She was subsequently started on carfilzomib (proteasome inhibitor) and dexamethasone with a slight decrease in her total IgG. However, she has recently developed nodules on her left lower extremity and the scalp, concerning for progressive disease.

DISCUSSION
Cutaneous lesions are a rare manifestation of multiple myeloma (MM) and are typically associated with a high tumor burden and a poor prognosis. Most lesions are thought to be due to cutaneous extension of underlying bone disease. However, lesions in the skin can rarely occur early in the course or be the first systemic manifestation of the disease via lymphatic or hematologic metastatic extension. Cutaneous lesions are most often associated with the IgG subtype, one of the most common immunoglobulins in MM, but have been seen in all immunological subtypes of MM except IgE. Although patients have been reported to survive years after developing cutaneous lesions, death typically occurs within 12 months after diagnosis.

Histopathologically, two patterns have been described: a more common nodular pattern with clusters of neoplastic cells and a diffuse interstitial pattern, with strands and cords of neoplastic cells arranged around collagen bundles. The plasma cells are pleomorphic, or in one case, spindle shaped. A grenz zone is frequently present. Russell bodies and Dutcher bodies are variably present. The neoplastic cells are CD79a, CD139, and epithelial membrane antigen (EMA) positive. The immunoglobulin and light chain type of the cutaneous population correspond with the serum immunoelectrophoresis studies.

The pathogenesis of the metastatic cells is still under investigation. While PCR studies from patients with HIV have found genomic sequences of HHV-8 and EBV in the neoplastic population, suggesting a viral etiology, this has not been demonstrated in patients without HIV.

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PRESENTERS
Edidiong Celestine Ntuen Kaminska, MD, MBS, Sonya Kenkare, MD, Vesna Petronic-Rosic, MD, MSc, Maria M. Tsoukas, MD, PhD

HISTORY OF PRESENT ILLNESS
A 46-year-old African American male presented with a three-to-four day history of new painful lesions on his scalp and lower extremities. Other reported symptoms included a productive cough and chest pain; the patient denied fevers or chills. His past medical history was significant for a heart transplant four months prior to presentation followed by transplant rejection two weeks after the transplant.

PAST MEDICAL HISTORY
Gout
Heart transplant
Hypertension

FAMILY HISTORY
Unremarkable

MEDICATIONS
Amlodipine, calcium, famotidine, folic acid, mycophenalate mofetil, prednisone, tacrolimus, sulfamethoxazole-trimethoprim, and valganciclovir

ALLERGIES
None

PHYSICAL EXAMINATION
The patient was a well-appearing male in no distress. Physical examination disclosed a gelatinous, necrotic, and tender papule with a central eschar on the left lower extremity and violaceous nodules on the scalp and thigh.

DERMATOPATHOLOGY
A 4-mm punch biopsy specimen from the left leg displayed a dense, diffuse mixed inflammatory infiltrate composed of neutrophils, lymphocytes, histiocytes, and extravasated erythrocytes in the dermis. Within the infiltrate, numerous fungal elements were identified. A periodic acid-Schiff stain and methenamine silver stain confirmed many septate hyphae and fungal elements.

RADIOLOGY DATA
Chest x-ray of the lungs: Near complete opacification of the right upper lobe associated with right sided volume loss and patchy left mid zone opacities

LABORATORY DATA
Complete blood count: Leukocytes 4.9 K/µL (4.5-11.0), hemoglobin 8.6 g/dL (13.5-17.5), platelets 141 K/µL (150-450)
Sputum and tissue cultures: Filamentous fungus consistent with *Aspergillus fumigatus*

DIAGNOSIS
Invasive aspergillosis in an immunosuppressed patient

TREATMENT AND COURSE
Prior to speciation, the patient was treated with empiric antifungal and antibacterial coverage with voriconazole, vancomyocin, cefepime, and metronidazole. Once the organism was identified the regimen

was changed to liposomal amphotericin B and micafungin. Despite appropriate treatment, the patient died seven days after presentation.

DISCUSSION

Invasive fungal infections (IFI) continue to be a major cause of morbidity and mortality in solid organ transplant recipients. The most common pathogens causing IFI are Candida species, followed by Aspergillus and Cryptococcus. *Aspergillus fumigatus* is an opportunistic pathogen that causes 90% of invasive aspergilloses and it is associated with a 50%-95% mortality rate. Cutaneous aspergillosis is usually a secondary cutaneous infection in the course of hematogenous dissemination of systemic aspergillosis. Skin lesions occur in 5-10% of patients with disseminated aspergillosis. Primary cutaneous disease is rare, usually associated with trauma, and most commonly caused by *A flavus*, *terreus*, *niger* or *utus*.

Risk factors for secondary cutaneous aspergillosis include an immunosuppressed state such as: neutropenia from hematologic malignancy or chemotherapy, immunosuppressive therapy, and acquired immunodeficiency syndrome. In the immunocompromised host, the most common manifestation of an Aspergillus infection is invasive pulmonary aspergillosis characterized by hyphal invasion and destruction of pulmonary tissue. Hematogenous dissemination can follow and occurs in 20-50% of these patients. It most commonly involves the central nervous system and the gastrointestinal tract. However, secondary Aspergillus infection of the skin is possible even in the absence of clinically evident pulmonary aspergillosis.

The clinical presentation of cutaneous aspergillosis may differ based on an individual's immune status. It has been suggested that in immunocompromised patients, rapidly growing lesions with an area of central necrosis may be a typical clinical manifestation of cutaneous aspergillosis compared to immunocompetent patients where lesions appear as small, red discrete papules, sometimes with a pustule in the center of the papule.

Traditional first line treatment for disseminated and limited cutaneous aspergillosis is high-dose intravenous amphotericin B. Voriconazole is also approved as a first-line agent. Surgery may be used as an adjunctive therapeutic option in primary cutaneous aspergillosis. To avoid this infection, specimens from the respiratory tract, serum and urine should be examined mycologically prior to heart transplant. Although an optimal approach for prophylactic antifungal therapy has yet to be determined, preventative measures such as environmental controls and chemoprophylaxis may be beneficial in high-risk patients.

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PRESENTERS

Adaobi I. Nwaneshiudu, MD, PhD, Edidiong Celestine Ntuen Kaminska, MD, MBS, Vesna Petronic-Rosic, MD, MSc, Maria M. Tsoukas, MD, PhD

HISTORY OF PRESENT ILLNESS

A 55 year old hospitalized male presented with a new non-pruritic eruption on his trunk and extremities. Prior to his eruption, he suffered rapid onset of severe headaches, photophobia, neck stiffness, fever up to 104^{o}F, generalized weakness and diffuse muscle aches for 4-5 days duration. He had traveled with his wife to a cabin in a wooded area of Michigan City, IN, where he experienced a tick bite under his arm about 1 week before the onset of his symptoms. He also reported dysuria and increased urinary frequency for which he was treated with ceftriaxone for a presumed urinary tract infection.

PAST MEDICAL HISTORY

Diabetes mellitus

REVIEW OF SYSTEMS / FAMILY HISTORY / SOCIAL HISTORY

ROS: per HPI
Family history: Non contributory
Social history: Married

MEDICATIONS

Pregabalin 75mg four times a day, metformin 1000mg twice daily, linagliptin 5mg daily, glimepiride 2mg daily, multivitamins daily

ALLERGIES

No known drug allegies

PHYSICAL EXAMINATION

Multiple petechiae distributed on the dorsal feet, and the radial aspects of the hands bilaterally, including the palms and soles. Petechiae and scattered erythematous papules were present on his chest and back.

DERMATOPATHOLOGY

Histopathological assessment of a lesion on the right foot showed a basketweave stratum corneum, with slight acanthosis and focal spongiosis of the rest of the epidermis. Numerous extravasated erythrocytes were present in the dermal papillae and visible superficial to mid reticular dermis. There was a mild perivascular lymphocytic infiltrate in the superficial vessels, with fibrin within the walls, demonstrated by periodic-acid-schiff staining. Gram, methenamine silver, and Fite stains were negative for bacteria, fungi, and mycobacteria, respectively.

LABORATORY DATA

On initial presentation: Platelet count – 25,000
During hospitalization: Complete blood count – normal levels; serum electrolytes – normal levels
1st Rickettsial PCR serum panel (Labcorp): **RMSF IgM – 1.87 (<0.9 negative); IgG - negative**
2nd Rickettsial PCR serum panel (Focus diagnostics - 2 weeks following 1st Rickettsial PCR serum panel): **RMSF IgM >1:256 (<1:64 negative); IgG >1:256 (<1:64 negative)**
Ehrlichia Chaffeensis and Anaplasma Phagocytophilum IgM and IgG- negative
CSF : No organisms, WBC – 10 (<5/µL), RBC – 8 (0/µL), Neutrophils - 15 (<6%), glucose – 106 (50-70mg/dL), protein – 54 (15-45mg/dL)
Nasal swab – negative for influenza A and B, parainfluenza, respiratory syncytial virus, rhinovirus
Lyme titer – 3.21 (<0.75 EIA); Lyme IgG Western blot – negative

RPR – non reactive

DIAGNOSIS
Rocky Mountain spotted fever

TREATMENT AND COURSE
The patient was initially treated with broad spectrum antibiotics including vancomycin, azetreonam, levofloxacin and antivirals, including acyclovir, but was transitioned after 1 day to doxycycline 100mg twice daily intravenously for 6 days during hospitalization, which he continued orally after discharge for a total of 21 days. Lumbar puncture showed reactive leukocytosis, and no organisms (HSV DNA, VZV DNA, enterovirus RNA, or west nile virus antibodies). Assessment for Lyme disease was also essentially negative. During his hospital course, he went into atrial fibrillation, acute respiratory distress syndrome from pulmonary edema, and septic shock but ultimately recovered with appropriate management. On his follow up, his rash and systemic symptoms resolved.

DISCUSSION
Rocky mountain spotted fever (RMSF) is the most common rickettsial disease in the United States. This dermatologic emergency is caused by transmission of the obligate intracellular parasitic bacteria *Rickettsia rickettsii* by the American dog tick, *Dermatocentor variabilis* (in most of the country), the brown dog tick, *Rhipicephalus sanguineus*, or by the wood tick, *Dermatocentor andersoni* (prevalent in the western U.S.). The bacteria infect endothelial cells of vessels resulting in increased oxidative stress and subsequent vasculitis of the skin and organs.

Clinically, the typical symptoms occur after a tick bite and include fever, headache, abdominal pain, vomiting, which precede the skin eruption. Most patients develop a petechial eruption 1 week after the systemic symptoms although some patient may not have an associated rash. Up to 30% of patients don't report a history of tick exposure. Symptoms range from moderate to severe illness, including cardiovascular compromise, coma and death. The mortality of RMSF is ameliorated by early diagnosis and antibiotic treatment - from 20% to approximately 5%.

Histopathology typically demonstrates a small vessel vasculitis with extravasated red blood cells. Skin biopsy from a lesion can also facilitate detection of the organism by immunohistochemistry or polymerase chain reaction. This is most sensitive (up to 75%) prior to antibiotic treatment; however a negative result shouldn't preclude treatment in the right clinical setting.

An important consideration is that diagnostic serum tests frequently are negative in the first 7-10 days of the illness so diagnosis is predominantly based on history, clinical signs and symptoms, to facilitate early treatment, which is associated with increased survival. Serum tests are confirmatory of the diagnosis. Routine blood cultures don't detect the bacteria and require the facilities at specialized laboratories. The gold standard serologic test for diagnosis of RMSF is the indirect immunofluorescence assay (IFA) with *R. rickettsii* antigen, performed on two paired serum samples to demonstrate a significant (four-fold) rise in antibody titers. The first sample should be taken as early in the disease as possible, preferably in the first week of symptoms, and the second sample should be taken 2 to 4 weeks later. In our case, the patient's initial serology for RMSF showed a positive IgM but negative IgG but a second serum sample tested 2 weeks later was strongly positive for both immunoglobulins, verifying the diagnosis.
Previous evidence from an established animal model of Rocky Mountain spotted fever suggests selective modulation of anti-oxidant enzyme activities in the target host tissues after infection. In addition, studies of the molecular pathogenesis of Rickettsia species suggests that the autotransporter protein, rickettsial outer membrane protein B (rOmpB), which is crucial for bacterial invasion of host cells, constitutes a protective antigen for this group of pathogens. Monoclonal antibodies against this protein are sufficient to confer immunity *in vivo*.

First line treatment for RMSF is doxycycline. This is one of the few indications for the use of doxycycline in children. Chloramphenicol remains the recommended therapy for women during pregnancy, but whether *R rickettsii* can cross the placenta and adversely affect the fetus remains unknown. Survivors of rickettsial infections are considered immune to disease.

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PRESENTERS
Erica R. Aronson, MD, Min Deng, MD, Vesna Petronic-Rosic, MD, MSc, Bernhard Ortel, MD

HISTORY OF PRESENT ILLNESS
An otherwise healthy 47 year old white male presented to dermatology clinic with non-healing wounds that had been present for over six weeks. The patient works as an excavator, and had recently been working a job digging up dirt in Cook County. He noticed new pink lesions that began as small bumps and increased in size to become pruritic, tender, large, wart-like, draining growths. He presented to his PCP and was started on antibiotic treatment with oral cephalexin, then switched to trimethoprim-sulfamethoxazole; however, he continued to develop new lesions on his back, buttocks, extremities, and face. He presented to the Emergency Department where he was then switched to oral doxycycline and rifampin for presumed MRSA abscesses, and bacterial culture was obtained that demonstrated no growth. He was referred to infectious disease and was started on clindamycin. Despite these interventions the patient continued to develop new cutaneous lesions, as well as increasing night sweats.

PAST MEDICAL HISTORY
Patient is a smoker with a 45 pack year history.

FAMILY HISTORY
Significant only for hypertension.

MEDICATIONS
Recent courses of cephalexin, trimethoprim-sulfamethoxazole, doxycycline, rifampin, and amoxicillin/clavulinic acid.

ALLERGIES
NKDA

PHYSICAL EXAMINATION
Multiple well demarcated, raised plaques with verrucous surface, hemorrhagic crust and surrounding erythema on the cheek, back, and buttocks.

DERMATOPATHOLOGY
The epidermis shows pseudoepitheliomatous hyperplasia with neutrophilic microabscesses. Within the superficial and deep dermis there is a dense granulomatous infiltrate with neutrophilic microabscesses. GMS and PAS stains show broad based budding yeast. The gram and fite stains were both negative.

LABORATORY DATA
Blastomycosis Antibody - Positive
Outisde CXR demonstrating lung nodules
Bacterial cultures demonstrated only *Staphylococcus epidermidis*
Fungal cultures did not yield any growth

DIAGNOSIS
Blastomycosis

TREATMENT AND COURSE
Before treatment could be initiated the patient transferred his care elsewhere.

DISCUSSION
Blastomycosis, also known as North American blastomycosis or Gilchrist disease, is an infection caused

by the thermally dimorphic fungus *Blastomyces dermatitidis*. Blastomycosis exists as a mold in the environment and as yeast in tissues. This fungus is commonly found in the humid environments of the Mississippi and Ohio River valleys as well as the Great Lakes region with most cases reported in the southeastern and south-central United States.
Blastomycosis may present in three forms: pulmonary, disseminated, or primary cutaneous disease. Most cases of cutaneous blastomycosis occur after lymphohematogenous spread from a primary pulmonary infection, even without evidence of overt pulmonary disease. Up to 50% of presumed cases of secondary or disseminated cutaneous blastomycosis lack associated findings on chest radiography. In these cases the pulmonary infection may have spontaneously resolved. Primary cutaneous disease may occur after traumatic inoculation; however, these cases are rare and far outnumbered by disseminated cases with cutaneous involvement.

Unlike other fungal infections which tend to affect the immunocompromised host, blastomycosis is often seen in immunocompetent individuals, although disseminated disease is more common in an immunocompromised patient. People in endemic areas with occupational soil contact such as farming, construction, and carpentry have been shown to have an increased risk of developing blastomycosis. Pulmonary infection occurs by inhalation of conidia and is the most common predisposing factor for cutaneous disease. Cellular immunity controls the organisms once inhaled, but they may disseminate in the more resistant yeast form. Skin is the most frequent site of extrapulmonary dissemination followed by bone, the genitourinary and central nervous systems.

Two types of typical cutaneous lesions have been described in disseminated disease: a verrucous plaque with an atrophic, cribriform center often studded with pustules at the periphery or a pustule that rapidly progresses into an ulcer with heaped borders. Recently, multiple cases of blastomycosis presenting as a generalized pustular eruption have been reported in the literature.

Clinical presentation of blastomycosis can be variable often leading to a delay in diagnosis as was seen in our patient who was treated with multiple courses of antibiotics for presumed bacterial abscesses prior to diagnosis. Microscopic identification of the characteristic broad-based (4-5µm) budding *B.dermatitidis* in tissue, sputum, or exudates is diagnostic. Fungal culture can provide a definitive diagnosis but requires 2-4 weeks of incubation for growth. Serological tests have low sensitivity and specificity; therefore, a negative result cannot exclude a diagnosis of blastomycosis.

Itraconazole is typically the first choice among the azole antifungal agents used to treat mild-to-moderate disseminated blastomycosis without CNS involvement. Cure rates of 90% have been reported following a six month regimen of 200-400 mg per day of itraconazole. For disseminated disease with CNS involvement, life threatening pulmonary infections and infections in the immunocompromised or pregnant host, IV amphotericin B is administered.

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PRESENTERS
Juliana Basko-Plluska, MD, Christopher R. Shea, MD, Vesna Petronic-Rosic, MD, MSc

HISTORY OF PRESENT ILLNESS
A 61-year-old African American male presented with an 8-month history of a solitary, asymptomatic, slow-growing mass on the right thumb. The patient did not recall any preceding trauma. He denied similar growths in the past.

PAST MEDICAL/SURGICAL HISTORY
Colorectal cancer- diagnosed in 2004, status post colon resection and neoadjuvant chemoradiation therapy, currently in remission
Graves' disease, status post thyroidectomy
Hypertension
Asthma

REVIEW OF SYSTEMS/ FAMILY HISTORY/ SOCIAL HISTORY
Review of systems was negative.
Family and social history were non-contributory.

MEDICATIONS
Nifedipine 90mg PO daily, Levothyroxine 125mcg PO daily, Albuterol inhaler PRN

ALLERGIES
ACE inhibitors: cough

PHYSICAL EXAMINATION
Physical exam was notable for a 10 x 6 mm, firm, skin-colored, exophytic subungual nodule displacing the nail plate of the right thumb. There was no tenderness upon palpation. Full flexion and extension of the distal interphalangeal joint were preserved.

DERMATOPATHOLOGY
A shave biopsy specimen revealed compact hyperkeratosis overlying a thickened epidermis. Within the dermis, there was a circumscribed proliferation of spindled cells without high-grade atypia embedded within a myxocollagenous stroma. The spindled cells were strongly positive for CD34 and weakly positive for epithelial membrane antigen (EMA), but negative for S100 and smooth muscle actin.

LABORATORY/IMAGING DATA
None

DIAGNOSIS
Superficial acral fibromyxoma

TREATMENT AND COURSE
The patient was referred to orthopedic clinic. Complete surgical excision was performed. There is no recurrence of the tumor to date.

DISCUSSION
Superficial acral fibromyxoma is a rare, slow-growing soft tissue tumor, which is commonly located in the periungual and subungual regions of the fingers and toes in middle-aged adults, especially men. Fletcher et al. first described this tumor in a series of 37 cases in 2001. To date, less than 150 cases have

been reported. The tumor presents clinically as a dome-shaped, polypoid or verrucous, painless nodule, which may distort the nail bed. Although almost exclusively located on the digits, it may also occur on the palm, heel or ankle with rare cases occurring on the upper leg. The biological behavior of this neoplasm is not fully understood; although, it is thought to be benign. To date, malignant behavior or metastasis has not been reported. The recurrence rate is as high as 42% in the setting of positive margins; therefore, complete excision with long-term follow up is recommended.

Histologically, superficial acral fibromyxoma presents as a proliferation of spindle-shaped cells with a storiform and fascicular pattern embedded in a myxoid or collagenous matrix. An increased number of blood vessels and mast cells in the stroma are observed. Significant nuclear pleomorphism and mitotic activity are rare. Most tumors are poorly marginated. Tumor cells express CD34, with a frequent epithelial membrane antigen (EMA) and CD99 co-expression. Smooth muscle actin, cytokeratin and S100 are negative in almost all cases. Recently, immunoreactivity to CD10 and nestin have been demonstrated. Furthermore, a lipomatous component can rarely be found in some cases. The differential diagnosis includes myxoid neurofibroma, superficial angiomyxoma, myxoid dermatofibrosarcoma protuberans, low-grade myxofibrosarcoma, sclerosing perineuroma and acquired digital fibrokeratoma. Immunohistochemistry is a useful tool to distinguish between these acral soft tissue tumors.

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PRESENTERS
Sonya Kenkare, MD, Lawrence Levine, MD, Christopher R. Shea, MD, Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS
A 61 year-old Caucasian male presented with a greater than 20 year history of a nontender growth on the posterior left upper arm that was increasing in size gradually. For many years this growth was not noticeable to the patient. Excisional biopsy with wide margin was performed on this mass.

REVIEW OF SYSTEMS
The patient denied constitutional symptoms.

PAST MEDICAL HISTORY
None

MEDICATIONS
None

ALLERGIES
None

FAMILY HISTORY
The patient denied a family history of non-melanoma skin cancer.

SOCIAL HISTORY
The patient is a single archivist in a Ba'hai temple.

PHYSICAL EXAMINATION
On physical exam a 7cm soft, protuberant, mobile mass was noted on the posterior, upper left arm.

LABORATORY/IMAGING DATA
None

HISTOPATHOLOGY
Within the dermis and subcutis a large cystic nodule composed primarily of monomorphous, basaloid cells lacking notable atypia was seen. Eccrine-type ductules and hyalinized stroma are present. At the luminal surface of the lesion there are disarrayed foci composed of cells with considerable nuclear atypia and exhibiting focal necrosis. Rare mitotic figures are identified. There are areas of microscopic infiltration at the periphery of the tumor.

DIAGNOSIS
Eccrine poromatous tumor with atypia

TREATMENT AND COURSE
The patient was referred to oncology and orthopaedics where MRI imaging was performed. No local invasion to bone or lymph nodes was noted and sentinel lymph node biopsy was deferred in favor of close clinical monitoring.

DISCUSSION
Eccrine poromas are rare, benign adnexal tumors derived from the acrosyringium. First reported by Pinkus et al. in 1956, eccrine poromas are believed to comprise 10 percent of all sweat gland tumors. Generally they occur in the middle aged and elderly, rare in childhood. Clinical diagnosis of eccrine

poromas may be challenging due to their polymorphic nature. They may appear similar to pyogenic granulomas, skin tags, warts, cysts or other adnexal tumors. Eccrine poromas are usually solitary, slow-growing, skin-colored or red papules or nodules on acral surfaces. They have also been seen on the extremities, head and neck and at past burn sites. Pigmented poromas and erythematous lesion have also been reported. Surface erosion or ulceration, presumably secondary to trauma, have also been noted.

Histologically, poromas demonstrate solid masses of uniform, cuboidal epithelial cells with ample cytoplasm and focal duct differentiation. The cells are small that the contiguous epidermis and tend to arrange themselves in cords and broad columns. Keratins 1 and 10 are expressed in the tumor nests. Rarely, divergent adnexal differentiation is noted in eccrine poromas with focal sebaceous, pilar and even apocrine differentiation. Due to the common embryological origin of follicular, sebaceous and apocrine structures, it has been suggested that some eccrine poromas may be of apocrine origin.

Malignant change in eccrine poromata has been noted in the literature. Eccrine porocarcinoma has been reported in a limited number of patients. The p53 gene has been implicated in porocarcinoma oncogenesis. The lower extremity was the most common site for porocarcinoma. The histologic diagnosis of eccrine porocarcinoma is made on the basis of an irregular tumor at least partly formed of characteristic poromatous basaloid epithelial cells displaying ductal differentiation, and significant cytologic atypia. A more aggressive clinical course may be indicated by more than 14 mitoses per high power field lymphovascular invasion by tumor, and depth >7 mm. It has also been suggested that tumors presenting an "infiltrative" advancing margin are particularly prone to local recurrence and require wide excision.

Our patient represents a unique clinical presentation. On histopathology, necrosis, cytologic atypia, rare mitotic figures and an infiltrative growth pattern at the periphery were noted. However, this neoplasm had a very large size at the time of presentation that was the result of slow growth over the course of many years. Upon consideration of these factors, the atypia noted in our patient's eccrine neoplasm was likely representative of degeneration due to ischemia rather than malignant transformation.

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