Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, November 14, 2012

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

Program

Conference Locations

Feinberg Pavilion Conference Center, 3rd Floor; 251 E. Huron St.; Chicago
Dermatology Clinic, 676 N. Saint Clair Suite 1600

8:30 a.m.	**Registration & Continental Breakfast with the exhibitors** *Feinberg Pavilion Foyer outside conference room "A" - 3rd Floor*
9:00 a.m. - 10:00 a.m.	**Resident Lecture** – *Feinberg A - 3rd Floor* "Update on Cutaneous Lymphomas" *Elise A. Olsen, MD*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** Patient, Poster & Viewing *Dermatology Clinic, Suite 1600, 676 N. Saint Clair*
11:00 a.m. - 12:00 p.m.	**General Session** - *Feinberg A - 3rd Floor* BLUEFARB LECTURE: "Female Pattern Hair Loss" *Elise A. Olsen, MD*
12:00 p.m. - 12:40 p.m.	**Box Lunches & visit with exhibitors** *Feinberg Pavilion Atrium*
12:40 p.m. - 1:00 p.m.	**CDS Business meeting** – *Feinberg A* – Presentation on Maintenance of Certification (Dr. Paller) – CDS business items
1:00 p.m. - 2:30 p.m.	**Case Discussions** – *Feinberg A*
2:30 p.m.	**Meeting adjourns**

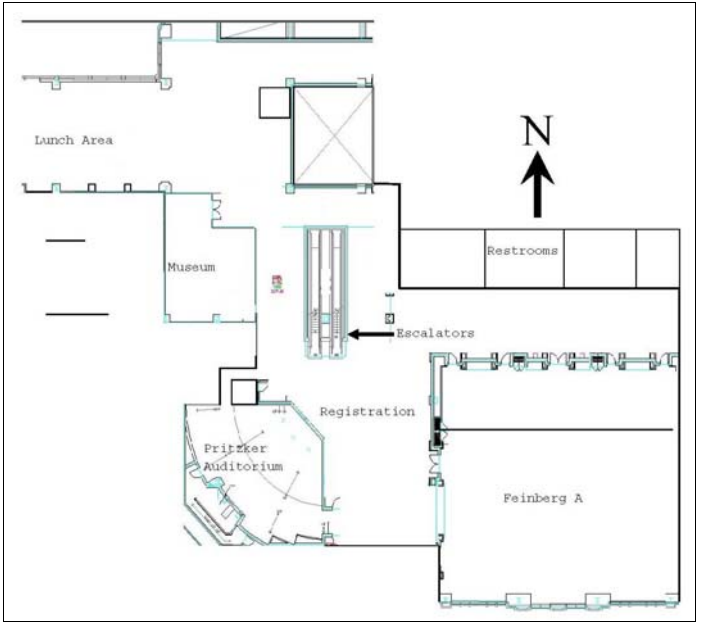
Mark the Date!

Next CDS monthly meeting – SATURDAY, December 8, 2012 at the University of Chicago; Steven R. Feldman, MD, PhD; Wake Forest Baptist Medical Center; Winston-Salem, NC

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

Feinberg Pavilion
3rd Floor layout

To Derm Clinic



Guest Speaker

ELISE A. OLSEN, MD

Professor of Dermatology and Oncology
Duke University Medical Center
Durham, NC

Delivering the Samuel Bluefarb Lecture

Dr. Olsen is Professor of Dermatology and Oncology at Duke University Medical Center in Durham, NC. She earned her medical degree at Baylor College of Medicine in Houston, TX (1978). She completed a residency in Internal Medicine at the University of North Carolina Memorial Hospital (1980) and in Dermatology at Duke Univeristy Medical Center (1983).

Dr. Olsen's clinical interests include cutaeous T- and B-cell lymphoma and other T-cell- infiltrative skin disorders; hair disorders, including hair loss and hair overgrowth (hirsutism).

Among her research interests, Dr. Olsen started a clinical trials unit, the Duke Dermatopharmacology Study Center, in 1983 which has been involved in more than 110 clinical studies for dermatological indications.

Financial Disclosures: Dr. Olsen reported the following grant/research support: Johnson & Johnson, Elsai.

Continuing Education Credit

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Conference"

November 14, 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. Discuss the most common types of female pattern hair loss and the physiological causes.
2. Describe the therapeutic and cosmetic options available for patients with this condition and discuss when each of these options are most appropriate.

.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

Elise A. Olsen	Grant Research: Johnson & Johnson and Eisai

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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Department of Dermatology

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Benjamin Marks, MD, PhD

Second Year
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Julia Minocha, MD
Lisa Shen, MD
Jennifer Sorrell, MD

First Year
Lauren Graham, MD
Lisa (Luzheng) Liu, MD
Pedram Yazdan, MD

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CHICAGO DERMATOLOGICAL SOCIETY **Case #1**

Presented by Pedram Yazdan, MD, Maria Colavincenzo, MD, and Joan Guitart, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 33 year-old African American female was diagnosed with Stage IB, CD8-positive hypopigmented mycosis fungoides (MF) in July of 2004. Three months after this diagnosis, she noted a patch of alopecia on her right frontal scalp. A scalp biopsy performed at an outside institution revealed "folliculocentric MF." In January of 2005, the MF on her body was noted to be in remission but the alopecia persisted. She was lost to follow up for the next 6 years. In 2011 she returned with several hypopigmented MF patches on the extremities as well as a persistent large patch of alopecia on her right scalp, for which a scalp biopsy was performed.

PAST MEDICAL HISTORY:
Eczema since age 14

MEDICATIONS:
Clobetasol ointment 0.05% nightly under occlusion to alopecic area of scalp

FAMILY HISTORY:
Mother and father with androgenetic alopecia, mother and sister with eczema

PHYSICAL EXAM:
The right frontal scalp was notable for a well-defined, 9cm x 5cm, patch of alopecia without hypopigmentation, erythema or scarring. The forearms and upper lateral thighs had several scattered ill-defined hypopigmented patches. No loss of eyebrow hair, nail changes or lymphadenopathy were noted.

LABs/Imaging:
Abnormal/negative: T-cell gene rearrangement by PCR on the right lower abdomen biopsy was positive for the presence of a T-cell clone.

Normal: CBC w/differential, BMP, LFTs, LDH, and Sezary cell count. T-cell gene rearrangement by PCR on the scalp skin biopsy was negative for the presence of a T-cell clone

HISTOPATHOLOGY:
Vertical and horizontal scalp biopsy sections reveal decreased number of hair follicles with increased numbers of catagen/telogen hairs as well as miniaturized follicular units. In the vertical sections a superficial band-like atypical lymphoid infiltrate with prominent epidermotropism was noted. The atypical lymphocytes were intermediate in size with hyperconvoluted nuclear detail. The bulb portion of several hair follicles was surrounded and infiltrated by the atypical lymphocytes. The intraepidermal and bulbar lymphocyes were predominantly CD8 positive. Dermal fibroplasia, interface changes or mucinous degeneration of the hair follicles were not identified.

DIAGNOSIS:
CD8-positive Mycosis Fungoides Masquerading as Alopecia Areata

TREATMENT AND COURSE:
Topical bexarotene and triamcinolone were used for her patch lesions with minimal success. Although NBUVB was tried for a few months in 2004, it was discontinued due to inconvenience

and insurance issues. She notes inconsistent use of tanning beds as well as outdoor sunlight exposure aimed at treating her MF lesions. Her alopecia has been treated in the past with betamethasone valerate foam without benefit. Currently she is using clobetasol ointment once daily under occlusion for her alopecia. Over the past 12 months, she has also undergone 2 injections of triamcinolone acetonide solution to her scalp. She continues to have several hypopigmented MF patches on her extremities and minimal hair re-growth on her scalp.

DISCUSSION:

Alopecia areata is an autoimmune disease characterized by a benign peri-follicular and intra-follicular T-cell infiltrate that affects anagen-stage hair follicles. Patients typically present with patchy hair loss without evidence of scarring or appreciable epidermal change. Alopecia areata can progress to alopecia totalis or alopecia universalis. The alopecia results from inflammation-induced damage of the follicle whereby the hair shaft can no longer remain firmly anchored in the hair canal and is rapidly shed or easily broken. A peri-follicular and peri-bulbar infiltrate of activated CD4+ cells is thought to facilitate the cytotoxic functions of activated CD8+ cells in the intrafollicular infiltrate. However, the hair follicle retains its capacity to regenerate and continue cycling since the hair-follicle stem cells are generally not destroyed. Thus, the alopecia is, in principle, reversible.

Alopecia occurring as the result of cutaneous lymphoma is an uncommon phenomenon but has been reported to occur in conventional patch/plaque stage MF and folliculotropic MF. Changes resembling alopecia areata have also been reported whereby the atypical lymphocytes infiltrate the follicular epithelium and, in some cases, involve the epidermal compartment. In all such cases, where scalp biopsies have been performed, the atypical lymphoid infiltrate is comprised of a predominance of CD4-positive lymphocytes over the CD8-positive cells. This is the first report of a CD8-positive mycosis fungoides causing alopecia areata-like changes.

Current treatments for patch stage MF include topical corticosteroids, topical mechlorethamine, topical bexarotene, narrow-band UVB, and PUVA. Topical treatments for alopecia areata include corticosteroids, intralesional corticosteroid injections, topical application of contact allergens including diphenylcyclopropenone and squaric acid, anthralin, excimer laser and PUVA turban. Systemic treatments for alopecia areata include oral corticosteroids, methotrexate, and cyclosporine.

Although alopecia areata can occur as a separate disease process in patients with cutaneous lymphoma, the findings in this case, and other similar reported cases, support the hypothesis that alopecia may result from follicular involvement with either a benign T-cell infiltrate (i.e., alopecia areata) or malignant lymphocytes (i.e., MF). Hence, clinical suspicion is warranted when evaluating patients with a known history of cutaneous lymphoma who present with alopecia areata-like hair loss. In such cases a biopsy should be considered in order to further evaluate the nature of the hair loss.

References:

1) Gilhar A, Etzioni A, Paus R. Alopecia areata. N Engl J Med. 2012 Apr 19;366(16):1515-25.
2) Iorizzo M, et al. Folliculotropic mycosis fungoides masquerading as alopecia areata. J Am Acad Dermatol. 2010 Aug;63(2):e50-2.
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4) Gerami P, et al. Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma. Arch Derm. 2008 Jun;144(6):738-46.

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 2**

Presented by Nilanthi Gunawardane, MD and Joan Guitart, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

This 12-year-old female presented to our clinic with a 2 month history of painful red plaques on her lower extremities. She initially saw a local dermatologist, who performed a biopsy that was read as panniculitis. She subsequently underwent an extensive infectious and rheumatologic work up, which was negative. Since that time, she has developed additional lesions on her bilateral lower legs along with persistent fevers, fatigue, night sweats and a 20lb weight loss.

PAST MEDICAL HISTORY

Previously healthy

FAMILY HISTORY

Sister with an 11q deletion associated with cyclic vomiting, thrombocytopenia and platelet dysfunction

PHYSICAL EXAM

Examination of the bilateral lower extremities was notable for numerous non-tender hyperpigmented firm subcutaneous nodules without ulceration or drainage. There was no cervical, axillary or inguinal lymphadenopathy. No hepatosplenomegaly was noted.

LABs/IMAGING

Abnormal: ESR 34, CRP 2.2
Normal/negative: CBC with differential, CMP, EBV IgG/IgM, Borrelia antibody, ACE level, ASO, PPD, CMV IgG/IgM, Blastomycosis antibody and urine antigen, histoplasmosis antibody and urine antigen, alpha-1 antitrypsin, ANA, aldolase, CK, bacterial, fungal and mycobacterial tissue culture

PET-CT: Hypermetabolic subcutaneous lesions extending from the ankles to the pelvis. Mildly hypermetabolic lymph nodes in the inguinal regions likely representing lymphomatous involvement.
Bone marrow biopsy: Moderate lymphopenia, normal absolute B cell count and moderately decreased CD4 and CD8 cells. Cytotoxic lymphocyte subsets demonstrate normal expression levels and profiles of granzyme A, perforin and granzyme B. There are defects in T and NK cell numbers.

HISTOPATHOLOGY

Right thigh: The sections reveal a dense lymphoid infiltrate involving the subcutaneous tissue. The epidermis shows interface features with small round lymphocytes along the dermal-epidermal junction, but without atypia. The dermis shows some edema and a patchy lymphohistiocytic infiltrate. The subcutaneous tissue also shows extensive necrosis with rimming of atypical lymphocytes. The cells are pleomorphic intermediate with irregular chromatin distribution. Scattered histiocytes, neutrophils and plasma cells are also noted. The infiltrate is composed of primarily T cells (CD3 positive) with a few scattered B cells (CD20 positive). The rimming lymphocytes are mostly CD4, CD5 and CD8 negative. However, there are numerous histiocytes (CD 163+) which are also staining for CD4. BF-1 and Gamma chain (GM-1) stains less than ½ of the T cells. TIA-1 is strongly positive. CD7 is partially retained. EBER-1 in situ hybridization was negative for Epstein-Barr mRNA.

DIAGNOSIS

Atypical subcutaneous lymphoid infiltrate consistent with gamma-delta T-cell lymphoma

TREATMENT AND COURSE

The patient was started on prednisone (40mg) at an outside hospital, with improvement of the cutaneous lesions and resolution of her fevers. Following the diagnosis of gamma-delta T cell lymphoma, the patient was started on 4 cycles of CHOP-E (cyclophosphamide, doxorubicin, vincristine, prednisone and etoposide). The team is considering reduced-intensity allogeneic hematopoietic stem cell transplant as the next step in her treatment regimen. Her sister is a perfect match.

DISCUSSION

Gamma-delta T cells represent less than 5% of all lymphocytes in the blood. These cells play an important role in innate immunity and are located predominantly in the epidermis and the GI tract. The most recent WHO classification for myeloid and lymphoid neoplasias defines cutaneous gamma delta T cell lymphoma (CGDTCL) as a monoclonal proliferation of activated gamma-delta T cells with a cytotoxic phenotype. CGDTCL is a very rare and highly aggressive entity with a variable clinical and histopathologic presentation that can significantly complicate diagnosis.

Patients with CGDTCL present with indurated plaques, nodules and tumors with ulceration and necrosis, most commonly on the legs followed by the trunk and arms. The median age at diagnosis is approximately 61 and the childhood onset of disease is extremely rare. The clinical differential diagnosis frequently includes panniculitis, but lesions can also mimic psoriasis or mycosis fungoides. Constitutional symptoms such as fever, weight loss and fatigue are invariably present. LDH is frequently elevated but bone marrow involvement is uncommon. Hemophagocytic syndrome and CNS involvement can occur with resultant increased mortality.

On histopathology, medium to large sized atypical lymphocytes with coarse chromatin are seen. Gamma-delta T-cells exhibit a BF1^{-}, CD3^{+}, CD4^{-}, CD5^{-}, CD7^{+}, CD8^{+}, CD45RA-, gamma M1+ phenotype. They stain positive for cytotoxic proteins (TIA-1, granzyme B, perforin) and usually exhibit a clonal rearrangement of the TCR gamma chain gene. GDTCL can present with a variable histopathologic pattern including epidermotropic, dermal and/or subcutaneous involvement. Multiple morphologies may co-exist in a single biopsy or in different specimens from the same patient. When prominent subcutaneous involvement is present, CGDTCL can mimic non-malignant conditions such as lupus panniculitis and multiple biopsies may be necessary to arrive at the correct diagnosis.

CGDTCL is an aggressive cutaneous malignancy with median survival ranging from 15-31 months. Of note, the degree of skin involvement does not appear to correlate with overall disease severity and prognosis. Radiation, immune therapy and multi-agent chemotherapy have all failed to consistently demonstrate sustained remission in affected patients. In adults, cytarabine and platinum-containing high intensive chemotherapy followed by AHSCT still remain first line therapy as these have historically been associated with the highest rates of cure. However, little is known about the natural history of this disease in children and this complicates treatment decisions. Our patient appears to be in complete remission after 4 cycles of CHOP-E and options for further management include AHSCT with myeloablative or reduced intensive conditioning versus a watch and wait approach following completion of 6 cycles of chemotherapy.

References:

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2. Tripodo, C., et al. Gamma-delta T-cell lymphomas. 2009. Nat Rev Clin Oncol. 6:707-717
3. Swerdlow, S.H., et al. WHO Classification of Tumours of haematopoietic and lymphoid tissues. 2008. IARC Press, Lyon. 302-303.
4. Koch, R., et al. Cutaneous gamma/delta T-cell lymphoma. 2009. J Dtsch Dermatol Ges. 7:1065-1067.
5. Chakrapani, A., et al. Primary Cutaneous Gamma Delta T-Cell Lymphoma With Brain Involvement and Hemophagocytic Syndrome. Am J Dermatopathol. 2012 Aug 2. [Epub ahead of print]

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 3**

Presented by Luzheng Lisa Liu, MD PhD, Simon Yoo, MD and Jonathan Cotliar, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

CASE A

HISTORY OF PRESENT ILLNESS

This 60 year-old Caucasian female presented with hundreds of basal cell carcinomas (BCCs) in the setting of known nevoid basal cell carcinoma syndrome (NBCCS) complicated by Chiari malformation and hydrocephalus. Her BCCs had been managed surgically until 2009, when she enrolled in our Phase II Vismodegib trial. She responded well; however she withdrew from the trial after 5 months due to alopecia resulting from the vismodegib. She returned to the clinic in 2011 with numerous new BCCs, 2 of which were subsequently excised. In August 2012, she returned with 3 large lesions on her scalp and numerous smaller lesions on the forehead and trunk.

PAST MEDICAL HISTORY

NBCCS (Chiari malformation, hydrocephalus, ovarian fibromas, cervical fusion, syrinx), migraines, deep vein thrombosis x 2, atrial fibrillation, cholelithiasis, non-obstructive nephrolithiasis.

MEDICATIONS

Hydrocodone/acetaminophen, warfarin

FAMILY HISTORY

Multiple family members with NBCCS, son died at the age of 2 from medulloblastoma.

PHYSICAL EXAM

The patient's cutaneous exam was notable for numerous hemorrhagic-crusted plaques on the scalp and eroded erythematous papules and plaques with rolled borders on the forehead, chest and back.

LABs/IMAGING

Negative/normal: CBC, BMP, LFTs, CK, Magnesium.

HISTOPATHOLOGY

Upper back: BCC

TREATMENT AND COURSE

The patient was restarted on vismodegib 150 mg daily on August 2nd, and has since noticed marked improvement of her skin lesions without significant side effects. She is taking magnesium supplementation and using topical minoxidil to prevent muscle cramps and alopecia, respectively.

CASE B

HISTORY OF PRESENT ILLNESS

This 48 year-old Caucasian female with NBCCS presented for Mohs surgery of a large BCC on her scalp. Due to the size of the lesion and significant scarring on the scalp from previous excisions and skin grafting, surgery was considered a poor option.

PAST MEDICAL HISTORY

NBCCS (complicated by multiple BCCs s/p excision, ovarian fibromas s/p bilateral oophorectomy, uterine fibroids s/p myomectomy), cutaneous squamous cell carcinoma

FAMILY HISTORY:
No known family members with NBCCS

PHYSICAL EXAM
The patient's cutaneous exam was notable for a 4.2 cm x 2.8 cm erythematous, ulcerated plaque on the right posterior scalp.

LABs/IMAGING
Positive/abnormal:
CT chest: two 3 mm pulmonary micronodules
CT brain: diffuse dural ossifications

Negative/normal: CBC, BMP, LFTs, Mg, CK

HISTOPATHOLOGY
Scalp: BCC, trichoepitheliomatous type

TREATMENT AND COURSE
As surgery was thought to be a poor option for this patient's locally advanced BCC on the scalp, she was enrolled in the phase II Vismobegib trial (150 mg/d) in February 2010. She had a dramatic response to vismodegib, with clinical resolution of all head, neck and trunk BCCs. At week 24, the lesion on the right posterior scalp was no longer ulcerated and biopsy of the lesion showed no residual BCC. She reported muscle cramps, intermittent diarrhea, diffuse alopecia (scalp, eyebrows, eyelashes and body), and fatigue. She remains enrolled in the trial.

CASE C
HISTORY OF PRESENT ILLNESS
This 73 year-old Caucasian female with a history of treatment with Grenz rays in the 1960s presented for Mohs surgery of a nodular BCC on the left ear. The patient has developed over 50 non-melanoma skin cancers, mostly BCCs, following her radiation treatment for psoriasis. After 6 Mohs stages for the nodular BCC of the left ear, the margins remained positive for BCC. She was given the option of an otolaryngology referral for further surgery, which would likely necessitate partial removal of the left ear, or a trial of vismodegib.

PAST MEDICAL HISTORY
Psoriasis, over 50 non-melanoma skin cancers, hypertension, hypercholesteremia

MEDICATIONS
Hydrochlorothiazide, atorvastatin, fosinopril, alendronate sodium, calcium 500/vitamin D, tazarotene 0.05% gel

FAMILY HISTORY
Father had bone cancer, brother has hypertension.

PHYSICAL EXAM
The patient's cutaneous exam was notable for fibrinoid and hemorrhagic crust of the triangular fossa and mid-helical rim of left ear with deformity of the superior helix. Multiple erythematous papules and plaques with overlying silvery scale were also noted on the patient's back, extensor arms and extensor and posterior legs.

LABs/IMAGING
Positive/abnormal: Ca 10.7 mg/dl

Negative/normal: CBC, BMP, LFTs, CPK, aldolase

HISTOPATHOLOGY
Left helix: BCC, nodular type, ulcerated.

TREATMENT AND COURSE
The patient was started on vismodegib at 150 mg daily on June 27th. At the last visit on September 28th, the patient's left ear was well-healed. The patient also reported improvement of her psoriasis since she was started on vismodegib. She endorsed mild left leg muscle cramping at night, salty taste in her mouth and diffuse hair loss.

DISCUSSION
Dysregulated Sonic hedgehog (SHH) signaling is the pivotal molecular abnormality underlying both sporadic BCCs and the rare inherited disorder NBCCS, or Gorlin syndrome. The SHH pathway, normally inactive in adult tissues, is a regulator of cell growth and differentiation during embryogenesis. In the pathogenesis of BCC, the SHH pathway is aberrantly activated by loss-of-function mutations in the tumor suppressor gene encoding Patched homologue 1 (PTCH1) (90%), and/or gain-of-function mutations in the oncogene encoding Smoothened homologue (SMO) (10%), leading to development of BCCs. Although most BCCs are treated surgically, no effective therapy exists for metastatic BCCs (mBCCs)or locally advanced BCCs (laBCCs), clinically defined as lesions for which surgery is inappropriate because of multiple recurrences signaling a low likelihood of surgical cure or substantial anticipated postsurgical disfigurement.

Vismodegib (Erivedge, Genentech–Curis) is a new first-in-class orally administered small-molecule SHH pathway inhibitor approved by FDA in January 2012 for the treatment of laBCCs and mBCCs. It works by selectively binding to SMO and potently inhibiting abnormal signaling of the SHH pathway. FDA approval was based on the evaluation of 96 subjects with mBCCs (n=33) or laBCCs (n=63) at a dose of 150 mg/d (Erivance BCC trial). Median duration of treatment was 10.2 months. Reduction of tumor size or healing of visible tumors was noted in 30% of the mBCC cohort and 43% of the laBCC cohort. The median response duration in both arms was 7.6 months. In another ongoing phase II study of 41 patients with NBCCS, Tang et al showed that at 1 month, vismodegib use had reduced the hedgehog target-gene expression by 90% (P<0.001) and diminished tumor-cell proliferation. Overall, significant reduction of both the per-patient rate of new surgically eligible BCCs (2 vs. 29 cases per group per year, P<0.001), and the size of existing clinically significant BCCs (-65% vs. -11%, P=0.003) were observed in the Vismodegib group versus the placebo. In some patients, all BCCs clinically regressed.

The most common adverse events (AEs) associated with vismodegib are muscle spasms, alopecia, dysgeusia/ageusia, weight loss, fatigue, nausea, decrease in appetite and diarrhea. In the Erivance BCC trial and the BCCNS trial, 12% and 54% patients discontinued drug treatment owing to AEs, respectively. When vismodegib was withdrawn, dysgeusia and muscle cramps ceased within 1 month, and scalp and body hair started to regrow within 3 months. Fatal events were reported in 7 patients on Erivance trial including hypovolemic shock, myocardial infarction, meningeal disease, and ischemic stroke. All 7 patients had clinically significant risk factors or coexisting conditions at baseline, and the relationships between the study drug and the deaths were unknown.

BCCs frequently recur after vismodegib treatment is stopped, suggesting that either the clinically regressed tumors harbor residual tumor cells or that drug-tolerant tumor cells with "cancer stem cell" characteristics exist (primary resistance). Case A showed dramatic tumor regression after restarting vismodegib, which supports the possibility of residual subclinical tumor cells that are sensitive to vismodegib. The possibility of primary resistance of the tumor cells is supported by

the disease progression seen in 18% of mBCC patients in the Erivance trial. These patients had an increase of 20% or more in the tumor dimension, a new ulceration, or a new lesion despite the vismodegib treatment. Recently, a case series reported 5 patients (21% of the study cohort, 3 with Gorlin syndrome) with tumor regrowth within or immediately adjacent to the prior tumor bed of a vismodegib-responsive tumor while still undergoing treatment. This observation suggests secondary or acquired resistance of tumor cells. The mean time to detect clinical regrowth was 56.4 weeks.

Overall, vismodegib has demonstrated promising efficacy as a single agent in treating laBCCs and mBCCs. It was also shown to have clinical activity in treating bone-metastatic medulloblastoma. Currently a number of other agents (BMS-833923, LDE225, LEQ506, IPI926, and TAK-441) that target components of the SHH pathway are under investigation. It is not yet clear whether vismodegib or related drugs in development will be efficacious in SHH-activated internal cancers with other driver mutations. Another area in which future study is warranted is the use of topical formulations of SHH antagonists in patients with BCCs, for which discordant results have been reported in clinical trials to date.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 4**

Presented by Anne Goldsberry, MD MBA and Joaquin Brieva, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 5**

Presented by Lisa Shen, MD, Kenneth Gordon, MD, Amy Paller, MD and Anthony J. Mancini, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University and Lurie Children's Hospital

CASE A

HISTORY OF PRESENT ILLNESS

This 14 year-old girl with a history of Crohn's disease presented with a pruritic eruption approximately 15 months after initiating adalimumab therapy. She was started on adalimumab in February of 2008 for her inflammatory bowel disease. In the spring of 2009, she developed erythema nodosum on her legs, which resolved without intervention. The following summer, she noted pruritic, scaly, red lesions that started on her back and subsequently spread to her trunk, buttocks, scalp, and face. She also experienced secondary MSSA infections which resolved with oral antibiotics and had perianal cultures which were positive for Strep (non group A, G, or C). On presentation, her treatment regimen included calcipotriene 0.005% and betamethasone dipropionate 0.064% ointments BID and fluocinolone 0.01% oil BID to her scalp and posterior ears. She was also applying tacrolimus 0.1% ointment to the periorbital region as well as tobramycin 0.03% eye drops prescribed by ophthalmology.

PAST MEDICAL HISTORY

Crohn's disease (proximal small bowel and pancolitis), iron deficiency anemia, seasonal allergies, headaches (with normal workup by neurology), anxiety

MEDICATIONS

Adalimumab, 6-mercaptopurine, calcipotriene 0.005% and betamethasone dipropionate 0.064% ointment, fluocinolone 0.01% oil, tacrolimus 0.1% ointment , tobramycin 0.03% eye drops, fluoxetine,multivitamin with iron, cetirizine prn

FAMILY HISTORY

Mother and grandfather have psoriasis, no other history of cutaneous or autoimmune disease

PHYSICAL EXAM

The patient was well-appearing. Her scalp contained mild flaking scale throughout. She had xerosis and scale on the eyelids with significant periorbital edema. There were erythematous plaques and crust on the bilateral nasal ala. Well demarcated erythematous plaques with yellow scale were present on the posterior aspect of the ears. She had scaly erythematous plaques at the oral commissures. Numerous well demarcated circinate erythematous scaly papules and plaques were distributed throughout the trunk, upper extremities, and intergluteal cleft, some with overlying yellow crust. Her left great toe exhibited onychauxis of the nail with an adjacent erythematous scaly plaque with significant fissuring and crust. Other nails were uninvolved.

LABs/IMAGING

Normal: CBC, BMP, LFTs, ferritin

DIAGNOSIS

TNF inhibitor induced psoriasiform dermatitis

TREATMENT AND COURSE

Despite concern about a relationship between the adalimumab and the new eruption, the patient and her gastroenterologist were concerned about substituting the medication, given its

efficacy for the Crohn's disease after recalcitrance to other medications. Instead, the patient's psoriasiform dermatitis was managed with halobetasol, alclometasone, calcipotriene, and tacrolimus ointments. She was treated with numerous courses of oral antibiotics and mupirocin for bacterial superinfection. Given the morphologic similarity to acrodermatitis enteropathica in conjunction with her underlying inflammatory bowel disease, the patient was empirically started on zinc supplementation as well. The patient's adalimumab was eventually discontinued after several discussions in June 2011, and she started certolizumab and methotrexate. The certolizumab was eventually stopped but she remains on methotrexate. Both her inflammatory bowel disease and cutaneous eruption are now well controlled on methotrexate.

CASE B

HISTORY OF PRESENT ILLNESS

This 11 year-old boy with a history of Crohn's disease presented with a pruritic and painful eruption approximately two years after initiating infliximab therapy. He first developed redness and bumps on his right middle finger, which subsequently progressed to involve the index finger. He also noted scaly red lesions on the back, flank, and scalp. He later developed painful blisters on the soles of the feet which interfered with his ability to bear weight and required him to use assistive devices for walking. He also underwent workup for possible chronic multifocal osteomyelitis involving lower extremity pain, but without joint swelling or erythema. He was later diagnosed with a complex regional pain syndrome.

PAST MEDICAL HISTORY

Crohn's disease, Factor XII deficiency, osteoporosis

MEDICATIONS

Infliximab, Vitamin D, Multivitamin

PHYSICAL EXAM

The patient's scalp had numerous hyperkeratotic scaly punctate papules throughout, with some associated erythema. He had erythematous plaques with micaceous scale on the trunk and arms. His right dorsal hand had numerous erythematous scaly plaques over multiple DIPs. Several distal fingertips revealed marked edema with erythema, scaling and crusting. Nails demonstrated distal onycholysis with periungual erythema. At one point during his course, he developed large painful pustules over his bilateral plantar surfaces.

LABs/IMAGING

Abnormal: mild lymphopenia (24%, absolute lymphocyte count 2200/uL) with 7% double negative T cells; ESR 28

Normal: remainder of CBC within normal limits; HLA B27 negative

DIAGNOSIS

TNF inhibitor-induced acrodermatitis of Hallopeau and psoriasiform dermatitis

TREATMENT AND COURSE

The patient's psoriasiform dermatitis was managed at various times with topical clobetasol, mometasone, fluocinolone, alclometasone, tazarotene, calcipotriene and compounded LCD. A six week course of fluconazole 200mg daily was administered for the paronychia and possible Candida superinfection. Other treatments included NBUVB treatment and acupuncture. Discontinuation of infliximab was strongly encouraged, but his gastroenterologist was hesitant to do so because of the severity of his underlying bowel disease and failures of other past therapies. His infliximab was ultimately discontinued after human anti-chimeric antibodies were

found to be elevated. Since discontinuing the infliximab, his psoriasis has improved. The pain in his feet has also improved to the point that he no longer requires assistive devices for walking. He continues to have clinical remission of Crohn's disease despite being off infliximab. Of note, he has continued acupuncture treatments since discontinuing the infliximab.

DISCUSSION

Tumor necrosis factor (TNF) inhibitors have been used as an effective treatment for numerous conditions, including inflammatory bowel disease and moderate to severe psoriasis. However, a paradoxical association of TNF inhibitors with induction and exacerbation of psoriasis has been observed and reported in the literature. Wollina et al. reviewed 120 initial cases from the literature of TNF inhibitor induced psoriasis or psoriasiform dermatitis and demonstrated three distinct patterns of cutaneous reactions: induction of a psoriasiform eruption, exacerbation of a pre-existent psoriasis and induction of psoriasis in individuals who did not previously have the disorder.

As was seen in case #2, palmoplantar pustular psoriasis is a unique and well described presentation of TNF inhibitor-induced psoriasis. Ko et al reviewed 127 reported cases in the literature between 1990 and 2007 and found that palmoplantar pustular psoriasis was observed in 40.5% of the cases and plaque-type psoriasis was observed in 33.1%. Joyau et al. reviewed 57 similar cases in the French Pharmacovigilance Database and also described that the eruptions are often pustules occurring on the palms and/or soles (33.3%). Though the mechanism for this is not understood, Michaelsson et al. demonstrated decreased TNF staining in eccrine sweat glands of patients with palmoplantar pustular psoriasis compared to healthy controls. Collamer et al reviewed over 200 described cases of suspected TNF inhibitor induced or exacerbated psoriasis in the literature and noted that the lesions occurred after any length of TNF antagonist treatment and did not negatively affect drug response. Co-administration of immunosuppressive medications such as methotrexate and azathioprine were not shown to be protective against this adverse reaction.

The pathogenesis for the paradoxical association of psoriasis with TNF inhibitor therapy has yet to be elucidated. Many attribute this adverse reaction to disruption of balance between TNF and interferon-alpha (IFN-α), since IFN-α treatment has similarly been observed to induce or worsen psoriasis. Increased IFN-α expression has previously been demonstrated in the vasculature and perivascular lymphocytic infiltrate of patients who develop psoriatic lesions while on TNF inhibitor therapy. Plasmacytoid dendritic cells are specifically involved in the production of IFN-α. TNF normally inhibits plasmacytoid dendritic cell maturation, and thus TNF inhibition may promote unopposed IFN-α production. Other subsets of cases suggest an infectious etiology such as Chlamydia associated keratoderma blennorrhagicum or streptococcal activation of specific T cells. An autoimmune phenomenon has also been proposed. Finally, genetic polymorphisms in the tumor necrosis factor receptor II gene may play a role in determining which subsets of patients will develop this paradoxical reaction.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 6**

Presented by Lisa Arkin, MD and Amy Paller, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS:
This 15 year-old male with a longstanding history of severe atopic dermatitis and keratitis necessitating multiple modalities of therapy is presented today for discussion of management and side effects.

PAST MEDICAL HISTORY:
Atopic dermatitis, atopic keratitis with corneal scarring, asthma, food allergies

ALLERGIES:
Soy, egg, gluten, peanut, sesame seed, tree nut, whey, penicillin

FAMILY HISTORY:
Several family members with atopic diathesis

PHYSICAL EXAM:
The patient was noted to have severe xerosis throughout. Periorbitally there was marked edema and erythema, with numerous erythematous deeply excoriated and lichenified papules and plaques on the upper and lower extremities in the flexural areas, buttocks, groin, trunk, chest and abdomen. Shotty cervical and axillary lymphadenopathy was present.

LABs/Imaging:
Abnormal: CBC with 37% eosinophils (normal 0-5%), absolute number 3.781 (normal 0-0.725)

Normal: WBC, platelets, hemoglobin, CMP

TREATMENT AND COURSE
To be discussed.

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 7**

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

HISTORY OF PRESENT ILLNESS
This 16 year-old Indian male presented with an evolving tumor on the left pretibia for months. The patient had a long standing history of lichen planus since age 5. Treatment with different topical preparations, including super potent steroids, resulted in some improvement but no resolution.

FAMILY HISTORY
No history of lichen planus

PHYSICAL EXAM
There were numerous hyperpigmented lichenified hyperkeratotic nodules and plaques involving the lower legs, most prominent on the bilateral pretibia. A distinct 4 cm lichenified plaque with an eroded hyperkeratotic center and raised borders were noted on the middle third of the left pretibia.

LABs/IMAGING
Normal: CBC, BMP, LFTs, lipids, quantiferon gold

HISTOPATHOLOGY
Left pretibia: atypical squamous verrucous proliferation with lichenoid reaction. Gram stain showed numerous cocci within the cornified layer. HPV and DPAS were negative.

DIAGNOSIS
Verrucous Carcinoma arising from Hypertrophic Lichen Planus

TREATMENT AND COURSE
After the diagnosis of verrucous carcinoma, the patient underwent Mohs micrographic surgery. A total of 3 stages were taken. The final post-operative wound size was 4.0 cm in diameter and extended into the fat. The area was closed with a full thickness skin graft taken from his left inner arm. He was subsequently started on prednisone 7.5 mg daily. One month after starting prednisone, acitretin 25 mg PO daily and hydroxychloroquine 400 mg PO daily were added to his regimen with significant improvement. After approximately one year, the patient developed steroid induced acne and was tapered off the medication. The oral steroids were replaced with intralesional injections of triamcinolone. The patient continued to improve on this regiment. He stopped the acitretin and hydroxychloroquine this year. He currently returns to clinic for intralesional triamcinolone injections as needed to control symptomatic lesions.

DISCUSSION
Lichen planus (LP) is an idiopathic, chronic disease of the skin, mucous membranes, and hair follicles. While the etiology of LP is unknown, a growing body of evidence suggests a role for T cell-mediated damage to basal keratinocytes that express altered self-antigens on their surface. The disorder has been associated with a host of exposures including viral infections, particularly hepatitis C, medications, and dental materials. Patients may present with pruritic annular, linear, bullous, or atrophic lesions.

Hypertrophic lichen planus (aka lichen planus verrucosus) is a variant of LP. Hypertrophic LP is most commonly seen on the pretibial area. In comparison to classic LP, the lesions are larger, verrucous or hyperkeratotic, and at times have overlying scale.

Malignant transformation is well described in oral lichen planus, but the cause has yet to be elucidated. Epstein et al. reviewed numerous studies on oral LP and hypothesized that loss of heterozygosity in these lesions could facilitate the development of dysplasia. More recently, several case reports have reported neoplastic transformation in cutaneous lichen planus, although this is thought to be a rare event. A recent article in 2011 published 3 new cases of squamous cell carcinoma or verrucous carcinoma developing in lesions of hypertrophic LP, increasing the total number of cases reported in the literature to 91. Most of the reported cases have developed after a minimum of 10 years of chronic disease.

Treatment for hypertrophic lichen planus is challenging, as most lesions do not respond to topical therapy. The literature lacks large controlled studies of treatment efficacy but improvement has been reported with corticosteroids, acitretin, azathioprine, mycophenolate mofetil, methotrexate, and phototherapy. It is not known whether therapy for cutaneous or oral lesions impacts the risk of neoplastic transformation.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 8**

Presented by Jennifer Sorrell, MD and Joaquin Brieva, MD

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE #9**

Presented by Tracy Donahue, MD, Simon Yoo, MD, and Juan Guitart, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

This 46 year-old Hispanic female with a past medical history of type 1 diabetes mellitus requiring pancreatic and kidney transplants who presented to dermatologic surgery for excision of skin nodules. Three months prior to presentation, a subcutaneous nodule formed on her left forehead. She subsequently developed similar nodules on her right lateral breast, right inguinal crease, left antecubital fossa, left flank, and left lateral leg which were mildly tender to palpation.

PAST MEDICAL HISTORY

Diabetes mellitus type 1 diagnosed at age 17 and complicated by retinopathy (legally blind), chronic kidney disease, and hypertension; hypercholesterolemia; hypothyroidism; migraines

PAST SURGICAL HISTORY

Renal allogeneic transplantation (2001), pancreatic allogeneic transplant (2008), left eye capsulotomy (2000), multiple retinal surgeries

MEDICATIONS

Sirolimus 1 mg daily, tacrolimus 2 mg bid, esomeprazole 20 mg daily, simvastatin 40 mg QHS, amlodipine 5 mg daily, lisinopril 20 mg daily, metoprolol 75 mg bid, levothyroxine 100 mcg daily, calcium and vitamin D supplements

REVIEW OF SYSTEMS

The patient endorsed loss of appetite, malaise, diarrhea, and weight loss. She denied fever, chills, and night sweats.

PHYSICAL EXAM

On initial evaluation there were thirteen soft mobile subcutaneous nodules ranging 1 cm to 3 cm in diameter scattered on the face, extremities, and trunk. Palpable right inguinal lymphadenopathy was appreciated about one month after the initial examination.

LABs/IMAGING

Abnormal: Hb 9.8 g/dL (11.6-15.4 g/dL), Na 134 mEq/L (136-145 mEq/L), K 5.7 mEq/L (3.5-5.1 mEq/L), Bicarbonate 16 mEq/L (21-31 mEq/L), BUN 43 mg/dL (2-25 mg/dL), Cr 2.18 mg/dL (0-1.3 mg/dL), Total Protein 9.5 g/dL (6.4-8.9 g/dL), Uric Acid 7.9 mg/dL (2.3-7.6 mg/dL)
Serum Epstein Barr Virus qualitative PCR: 266,212 copies/mL (nl < 200 copies/mL).
Beta 2-microglobulin: 14 mg/L (nl 0.70-1.80 mg/L)
Serum protein electrophoresis: a restricted band was seen in the gamma region
Serum immunofixation panel: monoclonal IgA kappa 2740 mg/dL (70-400 mg/dL)
Monoclonal free kappa light chain: 1180 mg/dL (170-370 mg/dL).
Serum free kappa light chain: 5.72 mg/dL (0.33-1.94 mg/dL)
Serum free lambda light chain: 3.84 mg/dL (0.57-2.63 mg/dL)

Normal: WBC, LFTs, Mg, LDH, peripheral blood smear, sirolimus level, tacrolimus level, bone marrow chromosome hematolog and FISH, X-Ray bone survey, screening mammogram

Imaging:
CT scan of the chest, abdomen, and pelvis without contrast: numerous subcutaneous nodules as well as enlarged right external iliac and mesenteric lymph nodes

DEXA Bone Density: osteopenia

PET/CT: abnormal metabolic activity within the bilateral supraclavicular, left axillary, mediastinal, hilar, mesenteric, inferior retroperitoneal, and bilateral pelvic lymph nodes. There was extensive inguinal lymphadenopathy, especially on the right side. Metabolic activity was increased in multiple subcutaneous nodules involving the trunk, upper extremities, and lower extremities.

Bone Marrow: normocellular bone marrow with mildly increased plasma cells and occasional EBER positive cells. Flow cytometric immunophenotypic studies of the bone marrow aspirate reveal polytypic plasma cells.

HISTOPATHOLOGY
Left flank: unremarkable epidermis and dermis. Beneath and within the subcutaneous tissue are dense nodular aggregates composed primarily of plasma cells and plasmablastic cells. Some atypia and numerous mitoses are noted. Russell bodies or germinal centers are not identified. Immunohistochemistry revealed a ratio of light chains within normal limits, and light chain restriction was not demonstrated. CD20, CD56, CD30, and CD43 were negative while CD138 was partially positive. MUM-1 and EBER-1 in situ hybridization were strongly and diffusely positive. Plasma cells were weakly IgA positive and negative for IgM.

DIAGNOSIS
Post-transplant EBV-positive plasmacytoma-like lymphoproliferative disorder

TREATMENT AND COURSE
The patient continued to develop new subcutaneous nodules. She developed pain in her right leg and swelling in both legs. Tacrolimus was discontinued. The patient was started on lenalidomide, bortezomib, and dexamethasone with allopurinol and acyclovir prophylaxis. The patient noted dramatic decrease in the nodules two days after initiating chemotherapy.

DISCUSSION
Post-transplant lymphoproliferative disorder (PTLD) is a lymphoid proliferation found in patients on potent immunosuppressive drugs following solid organ or bone marrow transplants. The incidence of lymphoproliferative disorders is 30-50 times higher in transplant patients compared to the general population. Risk factors include length of immunosuppression, EBV positivity, and type of organ transplant (small bowel > lung >heart > liver>kidney).

PTLD can be categorized as early, polymorphic, or monomorphic. Early PTLD is typically seen in children and young adults within the first year of transplant. Lymph node specimens usually exhibit innocuous polytypic plasmacytic hyperplasia, EBV seronegativity, rare immunoblasts, and architectural preservation. Patients respond well to immunosuppression reduction alone. Polymorphic PTLD lesions show disruptive architecture and consist of a mixed infiltrate of plasma cells, immunoblasts, and lymphocytes of varying maturation. Monomorphic PTLD consists of lesions that destroy the surrounding tissue, exhibit minimal evidence of maturation, and display sufficient cytological and architectural atypia to qualify as a lymphoma.

Plasmacytoma-like PTLD is a rare variant of monomorphic PTLD with only a few cases reported in the literature. Histologically, it is characterized by a monoclonal proliferation of plasma cells and plasmablastic cells typically staining positive for CD138 and Epstein Barr Virus (EBV). In a German

PTLD registry of 182 patients in 2010, only 8 cases were classified as plasmacytoma-like PTLD. Our patient's skin biopsy specimen stained diffusely and strongly positive for EBER-1, and her serum carried a high EBV DNA-load in the peripheral blood compared to other cases in the literature. EBV is thought to possibly drive the monoclonal proliferation of plasma cells. Agents such as tacrolimus inhibit T cells, leaving plasma cell proliferation unchecked. In these immunosuppressed individuals, plasma cells latently infected with EBV begin to proliferate, leading to a monoclonal expansion. The clones are more prone to mutations and therefore, malignant transformation.

Plasmacytoma-like PTLD typically presents years after transplant (median 8 years, range 3 months to 26 years). It has been reported following kidney, lung, liver, heart, and small intestinal transplants. There is a case reported 12 years following a renal and pancreatic transplant for diabetes mellitus. Initial presentation may involve the initial allograph site, gastric mucosa, sinuses, liver, lymph nodes, pleura, muscle, or skin. PTLD presenting in the skin is rare and usually linked to lymph node or other organ involvement. Patients commonly present with paraproteinemia. Bone marrow involvement and osteolytic lesions are less common, differentiating this disease from multiple myeloma.

There is limited data on the clinical behavior and prognosis of plasmacytoma-like PTLD. Therapeutic approaches have included immunosuppression reduction (IR), local radiation, and chemotherapy. While IR may occasionally result in complete remission, graft rejection may occur in as many as 37% of patients. Rituximab monotherapy or in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) is commonly utilized in CD20-positive B-cell PTLD that does not respond to IR alone. In CD20-negative patients with localized disease, irradiation and surgical excision have been utilized with good results. For disseminated disease, anti-plasma cell chemotherapy such as PAD (bortezomib, doxorubicin, and dexamethasone) has induced disease remission. Combination therapy with lenalidomide, bortezomib, and dexamethasone has been used in newly diagnosed multiple myeloma, and to our knowledge, this regimen has not been reported for treatment of plasmacytoma-like PTLD. This regimen was chosen in our patient due to her paraproteinemia.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 10**

Presented by Gunilla Carlsson Thorn, MD, Shatil Amin, MD and Jonathan Cotliar, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 57 year-old African American man presented with a 30 year history of painful skin lesions. The patient noted that the lesions tend to begin as tender knots, which drain purulent fluid and become thick and crusted over time. The patient also noted a distant history of severe scarring acne as well as persistent bone pain, joint pain and morning stiffness.

PAST MEDICAL HISTORY
Diabetes mellitus, anemia, benign prostatic hypertrophy

MEDICATIONS
Insulin, metformin, ranitidine

FAMILY HISTORY
Several family members with "bad skin"

SOCIAL HISTORY
Two to three alcoholic drinks per week, 1 pack of cigarettes per week, distant history of heroin

PHYSICAL EXAM
There were several patches of scarring alopecia on the scalp and deep cribiform scarring over the bilateral cheeks, nose and forehead. On the right temple, left proximal medial arm and left proximal medial thigh were large fluctuant plaques with overlying cribiform ulcerations, thick overlying crusting and purulent drainage. The extremities had wide spread scarring and innumerable hyperpigmented vegetative nodules. The patient endorsed tenderness of the sternum to palpation.

LABS/IMAGING
Abnormal: Hgb 8.5, tissue culture grew multiple mixed microorganisms but no predominating pathogens

Bone Scintigraphy: Extensive periosteal reaction involving both femurs throughout their length consistent with hyperostosis

Negative/normal: BMP, LFTs, ANA, RF, HIV, hepatitis serologies, RPR, quantiferon gold, tissue fungus culture & stain, tissue mycobacteria culture & smear

HISTOPATHOLOGY
Right thigh: The sections reveal a markedly corrugated epidermis with irregular proliferative epithelial hyperplastic and reactive changes without evidence of nuclear atypia. There is a deep dermal infiltrate composed of lymphocytes, plasma cells and aggregates of neutrophils. The dermis also shows variable fibroplasia with some edema and telangiectasia. Acantholysis is not noted but there is some dyskeratosis associated with exocytosis of neutrophils. Immunohistochemistry for Treponema and special stains (DPAS, Gram and acid fast bacilli) were negative for microorganisms. Direct immunofluorescence was negative for immune deposits.

DIAGNOSIS
SAPHO Syndrome

TREATMENT AND COURSE

Our preferred treatment strategy is to start adalimumab; however, the patient's insurance denied coverage. We are currently attempting to get the medication at no cost to the patient through the Abbott Patient Assistance Foundation. In the meantime, symptomatic lesions are treated with intralesional triamcinolone acetonide suspension.

DISCUSSION

The syndrome of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) represents a rare constellation of chronic overlapping osteoarticular and cutaneous manifestations. The clinical presentation is heterogeneous and frequently incomplete, resulting in diagnostic difficulties. The typical cutaneous manifestations include palmoplantar pustulosis and severe acne, which can manifest as acne conglobata, acne fulminans or hidradenitis suppurativa. Pyoderma gangrenosum, Sweet's syndrome and other neutrophilic dermatoses can also be seen. Osseous involvement can range from osteitis with sclerosing features to hyperostosis with cortical thickening resulting from chronic periostal reaction. Erosive arthritis can also occur. Osteoarticular manifestations most commonly involve the anterior chest wall, especially the sternocostoclavicular region, but can also involve the spine, pelvic girdle, sacroiliac joints, peripheral joints, long bones or mandibles. These osteoarticular changes are best characterized by total body scintigraphy, but plain radiographs, computed tomography and magnetic resonance imaging studies can also be effective.

The pathogenesis of SAPHO syndrome remains poorly understood but likely involves infectious, genetic and immunologic mechanisms. A pathogenic role of *Propionibacterium acnes* (*P. acnes*) causing a reactive osteitis in genetically predisposed individuals has been proposed since the microbe has been isolated from bone biopsy specimens. However, it remains unclear if the osteoarticular changes seen in SAPHO syndrome are directly related to *P. acnes.* Associations with inflammatory cytokine overproduction and neutrophil dysfunction have also been reported.

SAPHO syndrome generally has a chronic and protracted course; however, the severity of the symptoms can vary greatly from person to person. Given the rarity of the disease and the lack of large controlled studies, treatment remains empiric to date. Non-steroidal anti-inflammatory agents and analgesics generally provide only modest improvement. Bisphosphonates can be used given their anti-inflammatory effects and their inhibition of bone resorption and turnover. Antimicrobial agents may be considered given the suspected role of *P. acnes*, but their efficacy remains anecdotal. Recently, treatment with TNF-alpha inhibitors and interleukin-1 receptor antagonists has shown promise for refractory cases.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE #11**

Presented by Benjamin Marks, MD, PhD and Simon Yoo, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 52 year-old female with a history of renal transplantation presented to our clinic for treatment of recalcitrant molluscum contagiosum on her face. Her renal failure was secondary to systemic sclerosis and she had received two renal transplants, one in 2003 and one in 2006. She had been maintained on tacrolimus and mycophenolate mofetil since that time and developed molluscum contagiosum in 2010. She was treated with serial cryotherapy, imiquimod, cimetidine and curettage but continued to develop more lesions on her lower face and upper neck.

PAST MEDICAL HISTORY
Systemic sclerosis with Raynauds and esophageal strictures, renal transplant (2003, 2006), hypothyroidism

MEDICATIONS
Verapamil, mycophenolate mofetil, tacrolimus, levothyroxine, valacyclovir

PHYSICAL EXAM
Chin, upper cutaneous lip and upper neck with ~30 umbilicated 2-3mm dome shaped papules

LABs/IMAGING
Normal renal function

HISTOPATHOLOGY
The specimen consists of small fragments of tissue showing parakeratotic material with focal inclusion eosinophilic bodies with eccentrically located nuclei.

DIAGNOSIS
Molluscum contagiousum in a renal transplant recipient

TREATMENT AND COURSE
The patient was started on 3% cidofovir compounded in unibase cream. As per the protocol of the previous published report by Toro *et al*, she applied the medication once a day, five days a week for eight weeks. After the first two weeks, the patient had a reduction in the size of the lesions but still had appreciable disfiguring disease. By five weeks of use, there was almost complete resolution of all lesions with some residual post inflammatory hyperpigmentation. After seven weeks of treatment, the patient had complete resolution of all lesions. She continued treatment for a total of eight weeks.

DISCUSSION
Renal transplant recipients suffer from a necessary iatrogenic immune suppressive state to prevent solid organ rejection. As such, renal transplant recipients are at a greater risk of developing common viral skin infections such as molluscum contagiosum, which is often recalcitrant to conventional therapy due to poor immune function.

Previous reports of successful treatment of molluscum contagiosum in transplant recipients include curettage and electrocauterization of lesions in the axillae and 5% imiquimod topical treatment to lesions on the face. The former report involved a cosmetically insensitive area, the

axillae, thus allowing for aggressive treatment without much concern for scarring, while the latter report took 6 months to completely clear the viral lesions. Thus, effective treatment options for molluscum contagiosum in cosmetically sensitive areas such as the face remain limited for immunosuppressed patients.

Cidofovir is a acyclic nucleoside phosphonate analog with broad spectrum antiviral activity against DNA viruses including HSV, adenovirus, poxvirus and papillomavirus. It is thought to act on viral replication by inhibiting viral DNA polymerase. There have been several reports of the use of the anti-viral cidofovir for recalcitrant molluscum contagiosum on the face of HIV infected individuals. Both topical and intravenous forms have been used with almost complete clearance of disease in several weeks. Intravenous cidofovir is associated with a significant risk of renal toxicity, reported in up to 40% of patients, but topical compounded cidofovir is thought to have minimal risk due to its low systemic bioavailability, reported as <0.2% on intact animal skin.

The patient was started on 3% cidofovir compounded in unibase cream once daily. She was completely clear of disease by eight weeks of treatment. Topical cidofovir appears to be safe and effective in virally induced states of immunosuppression such as in AIDS patients, as well as iatrogenic forms of immunosuppression including transplant recipients.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 12**

Presented by Lisa Arkin, MD, Emily Keimig, MD and Amy Paller, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS: This 6 year-old boy initially developed fever, sweats, arthritis, fatigue and abdominal pain and was found to have a pericardial and pleural effusion. He had a thorough work-up for lupus that was entirely negative and was presumptively diagnosed with systemic juvenile idiopathic arthritis. Several months later, he was noted to develop flesh colored papulonodules on his hands, predominantly occurring on the PIP, DIP and metacarpal joints, which subsequently spread to involve his feet. The lesions were asymptomatic but mildly sensitive to trauma. He noted persistent arthralgias in his hands and feet, but was otherwise feeling well.

PAST MEDICAL HISTORY
Allergic rhinitis, asthma

MEDICATIONS:
Diclofenac, loratadine, albuterol, mometasone nasal inhalation

FAMILY HISTORY:
No history of lupus, inflammatory bowel disease, thyroid disease, or other autoimmune disease

REVIEW OF SYSTEMS:
He denied transient rashes, oral ulcers, photosensitivity, hematuria, hair loss, mood changes, seizures, nausea, vomiting, constipation, chest pain, shortness of breath.

PHYSICAL EXAM
The patient was noted to have numerous exophytic and dome-shaped, flesh colored and faintly translucent papules involving the PIP and DIPs of numerous fingers on both the dorsal and ventral hands bilaterally, as well as the right foot. The left foot was clear. There was no edema or tenderness to palpation noted in the joints of his hands, feet, knees or ankles.

LABs/IMAGING
Abnormal: Hemoglobin 8.4 (nl 11.5-15.5), MCV 77 (normocytic), ferritin 186 (nl 22-322), fibrinogen 492 (nl 150-417) CRP 4.7 (nl <1.3), ESR 88 (nl 4-20)

Normal: WBC, platelets, CMP, ANA, anti-dsDNA, anti-Ro/La, anti-RNP, anti-Smith, Direct Coombs test, C3 and C4.

Right hand XR: soft tissue swelling, no other abnormalities

HISTOPATHOLOGY
R thumb: Sections reveal a dome shaped papule with intersecting fascicles of myofibroblastic cells along with individual fibroblasts in a collageneous stroma with mild perivascular inflammation. Myofibroblasts stain strongly with SMA, CD30 labels the blood vessels, and EMA is unremarkable. Trichrome shows no perinuclear inclusions.

DIAGNOSIS
Fibroblastic rheumatism

TREATMENT AND COURSE

The cutaneous lesions, their histopathologic features, and associated arthralgias led to the diagnosis of fibroblastic rheumatism. The patient was started on methotrexate 10 mg weekly in conjunction with folic acid and a slow prednisone taper, with significant improvement (but not yet clearance) after several months of therapy.

DISCUSSION

Fibroblastic rheumatism was first described by Chaouat in a small cohort of patients with symmetric polyarthritis and cutaneous nodules on the dorsal aspect of the hands, elbows and knees. Fewer than 30 patients have been reported to date, a third of whom were children. Cutaneous flesh-colored nodules are invariably present and typically occur on the dorsal aspect of the hands, elbows and knees, although they also have been described on the ears and neck. The associated arthritis can be rapidly progressive and erosive, producing irreversible joint destruction. Additional findings may include sclerodactyly, joint or fascial contractions, and Raynauds phenomenon. Visceral involvement has not been reported, and it is unclear whether our patient carries the diagnosis of both fibroblastic rheumatism *and* systemic juvenile idiopathic arthritis, or more likely, that he had fibroblastic activation producing inflammation in his heart and lungs. Early diagnosis and treatment are vital to prevent disabling joint sequelae.

The clinical differential diagnosis can include multicentric reticulohisiocytosis, rheumatoid nodules, nodular scleroderma, fibromatosis, and erythema elevatum diutinum. For this reason, histopathologic evaluation of lesions is critical for diagnosis. Characteristic findings include a dense proliferation and fibroblasts and myofibroblasts, with thickened collagen and loss of elastic fibers. Acutely, inflammation is noted with a dense proliferation of fibroblasts, myelofibroblasts and mononuclear cells, while more chronic lesions demonstrate thickened collagen with dense dermal fibrosis and minimal inflammation. *In vitro*, the fibroblasts in fibroblastic rheumatism demonstrate an increased proliferative rate with diminished collagen production in contrast to systemic sclerosis, which is characterized by fibroblast proliferation with consequent increased collagen production. Synovial biopsies from a few patients with fibroblastic rheumatism have also confirmed fibroblast proliferation with synovial fibrosis.

The pathogenesis remains unknown but is speculated to involve an inflammatory or infectious trigger that produces fibroblastic and myofibroblastic proliferation, potentially through elaboration of cytokines, including TGF-beta. The course tends to wax and wane with significant functional loss in the setting of accumulating joint damage. Multiple therapeutic agents have been tried anecdotally, including systemic steroids, methotrexate, hydroxychloroquine, and colchicine. Methotrexate has been shown to reduce human synovial fibroblastic proliferation *in vitro* with dose-dependent responses. Given the known inflammatory stage of the disease process, early diagnosis and treatment may significantly modify the expression and course of the disease.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #13**

Presented by Tracy Donahue, MD, Mary Martini, MD, and Roopal V. Kundu, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

This 37 year-old healthy Southeast Asian female presented with a six-month history of skin hyperpigmentation. The asymptomatic macules and patches appeared soon after the application of a weight reduction body wrap at a medical spa (Table 1). She denied applying any other new products. She denied taking herbal remedies but endorsed ingesting soy and herbal teas as part of her regular diet.

Table 1. Ingredients in Weight Reduction Body Wrap

Aloe vera	Glycerin	Retinyl palmitate
Avocado pulp and extract	Glyceryl stearate	Sesame oil
Allantoin	Isopropyl myristate	Soy oil
Cassia (cinnamon)	Ivy extract	Stearic acid
Centella asiatica extract	Niacin	Tea extra
Ergocalciferol	Palmitic acid	Tetrasodium EDTA
Food grade preservatives	Panthenol	Triethanolamine
Garlic oil	Propylene glycol	

PAST MEDICAL HISTORY

Dry eyes

MEDICATIONS

Cyclosporine ophthalmic drops

PHYSICAL EXAM

Chest with ill-defined hyperpigmented macules and patches and well-demarcated linear hyperpigmented patches arranged horizontally on the back and thighs.

LABS

Negative/normal: CBC, BMP, ANA, TSH, tryptase, alpha-MSH, ACTH, morning cortisol level, Soybean IgE

HISTOPATHOLOGY

Biopsy of the back revealed minimal perivascular and interface inflammation with numerous melanin laden macrophages and scattered lymphocytes in the upper dermis, consistent with melanoderma due to post-inflammatory hyperpigmentation.

PATCH TESTING

Patch testing to standard, cosmetic, natural, and fragrance trays showed reactions to nickel (++), cinnamic aldehyde (+), and myristyl myristate (+). Cassia was negative.

PRICK TESTING

Prick testing to soy extract was negative.

DIAGNOSIS

Post-inflammatory hyperpigmentation secondary to allergic contact dermatitis

TREATMENT AND COURSE

A safe list of products was created using a Contact Allergen Replacement Database and provided to the patient. She was counseled to avoid exposure to her allergens, including a low-nickel diet. The hyperpigmentation partially faded on follow up several months later.

DISCUSSION

The patient's post-inflammatory hyperpigmentation is most likely related to an allergic contact dermatitis to ingredients found in the body wrap. Nickel, which is highly concentrated in soy, likely was the greatest contributor given her strong allergic response to nickel on patch testing. Nickel acts as an analog to copper and zinc in plants, which are essential plant nutrients absorbed from the soil and transported in xylem. Plant tissue contains more nickel than animal tissue, and plants high in nickel include soybeans, cocoa beans, legumes, and herbs found in green and black tea. Our patient endorsed eating a diet high in soy-content. Her negative soy prick test and serum IgE suggest the nickel content rather than the soy itself contributed to her skin findings.

Soy is frequently added to cosmeceuticals due to its anti-oxidant, anti-aging, and bleaching effects. Soybean trypsin inhibitor and Bowman-Birk protease inhibitor decrease hyperpigmentation by inhibiting keratinocyte protease-activated receptor 2 (PAR-2). PAR-2 activation facilitates contact between keratinocytes and melanocytes, enhancing the transfer of melanosomes. However, in our patient soy likely caused hyperpigmentation due to her nickel allergy.

The body wrap contained cassia (cinnamon), which comes from the bark of an evergreen tree of the family Lauraceae. Cassia extract contains several active components, including cinnamic aldehyde. Cassia and its components exhibit anti-inflammatory, anti-microbial, anti-oxidant, and anti-tumor activity. Cassia extract has been shown to enhance pro-apoptotic activity via the inhibition of NFkB and AP1 in a mouse melanoma model. Cinnamon oil contact dermatitis has been previously reported in association with a spa mud bath. While our patient patch tested negative to cassia, she was weakly allergic to cinnamic aldehyde. This discrepancy is likely due to the difference in cinnamic aldehyde concentrations in these two patches. The cinnamic aldehyde patch contains cinnamic aldehyde 10% whereas the cassia patch contains cinnamic aldehyde 0.25-0.5%. Unfortunately the body wrap manufacturer was unwilling to further define the concentration of cassia components in the body wrap ingredients. Given her allergic reaction to cinnamic aldehyde was weak on patch testing, exposure to cassia likely contributed minimally to her skin findings. Finally, our patient was weakly allergic to myristyl myristate. The ester form, isopropyl myristate, was used as an emollient in the body wrap. There has been a report of contact dermatitis due to isopropyl myristate in sunscreen.

We present this unusual presentation of post-inflammatory hyperpigmentation to draw attention to the potential for cosmeceutical-associated allergic contact dermatitis.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE #14**

Presented by Julia Minocha, MD and Joan Guitart, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 69 year-old female presented for evaluation of a lesion on her neck, which had appeared 1 year ago and was noted to be erythematous, scaly and warm to the touch with associated burning pain. She was treated with clotrimazole and betamethasone with improvement in the scaling but persistent pain. The patient also reported having 2 episodes of erythema nodosum during the last year. She denied fevers, chills, night sweats, or weight loss.

PAST MEDICAL HISTORY
Insomnia, colonic polyps

PAST SURGICAL HISTORY
Breast implants, hysterectomy, lap colectomy, herniorrhaphy

MEDICATIONS
Raloxifene, aspirin, zolpidem, multivitamin

FAMILY HISTORY
Psoriasis, breast cancer, no history of hematologic malignancy

PHYSICAL EXAM
An ill-defined erythematous patch was present on the vertex of the scalp and the anterior neck. There was no cervical, axillary, or inguinal lymphadenopathy.

LABS/IMAGING
Abnormal: EBV IgG – positive

Normal: CBC, CMP, LDH, hepatitis B/C serologies, HIV Ag/Ab, EBV IgM, EBV quantitative viral load, HTLV I/II IgG

Bone marrow biopsy – normocellular, no evidence of lymphoma, negative for clonal T cell receptor gene rearrangement

PET/CT – no definite evidence of active lymphomatous involvement, either within the lymph nodes, other organs, or the cutaneous tissues

HISTOPATHOLOGY
Right lateral neck: Mild acanthosis with exocytosis and spongiosis is noted. Atypical large cells are noted inside dilated lymphatic vessels (podoplanin and CD31 positive). Some atypical cells are also noted along the superficial plexus. The intravascular cells are CD2, CD3, CD4, CD5, BF1, CD30, and CD25 positive; and negative for CD8, CD20, ALK-1, CD7, Fox P3, cytokeratin (AE 1/3), CD68, CD45RA, CD45RA, gamma-delta TCR, and EBER-1 (EBV mRNA) in situ hybridization. No clonal T cell receptor gene rearrangement was detected.

DIAGNOSIS
CD30+ intravascular lymphoproliferative disorder

TREATMENT AND COURSE

The patient was treated with topical triamcinolone 0.1% ointment with near complete resolution of the lesion but continued subtle burning sensation.

DISCUSSION

CD30 is a cell membrane protein belonging to the tumor necrosis factor receptor family. It was originally identified on the surface of Reed-Sternberg cells and is now known to be expressed by activated T and B cells, endometrial cells, and eosinophils. The function of the CD30-CD30L complex has not been completely elucidated, however, it is believed to play a role in co-stimulatory functions, negative selection of T cells, CD8+ memory T cells, and the development of Th-2 responses.

A number of both benign and malignant cutaneous conditions have been described that are characterized histologically by a CD30+ lymphocytic infiltrate. The conditions can be categorized along a spectrum based on their clinical prognosis, with benign inflammatory or reactive conditions such as atopic dermatitis, cutaneous viral infections (parapox virus, herpes simplex virus, molluscum contagiosum), and drug reactions at one end of the spectrum, and neoplastic conditions with poor prognosis such as cutaneous Hodgkin's lymphoma and nodal anaplastic large cell lymphoma with cutaneous involvement at the other end. Primary cutaneous CD30+ lymphoproliferative disorders including lymphomatoid papulosis and primary cutaneous anaplastic large cell lymphoma lie in the middle of the continuum. In 2006, Kempf suggested that all benign reactive CD30+ lymphocytic infiltrates should be classified as CD30+ pseudolymphomas to clearly distinguish these disorders from the malignant CD30+ entities.

Intravascular lymphoma (otherwise known as angiotrophic lymphoma, angioendotheliomatosis proliferans systemata, intravascular lymphomatosis, malignant angioendotheliomatosis) is a rare extranodal non-Hodgkin's lymphoma with a poor prognosis, which typically affects patients in the sixth or seventh decade of life and is often diagnosed post-mortem. The intravascular malignant infiltrate is most commonly of B-cell origin; however, T-cell variants have been reported in approximately 25% of cases including rare cases of CD30+ T-cell infiltrates. There are only two case reports in the literature of atypical intravascular CD30+ lymphocytic infiltrates following a benign course consistent with a CD30+ pseudolymphoma. Bryant et al. reported the first case of an endometrial polyp with an intravascular proliferation of T cell lymphocytes suggestive of intravascular lymphoma, however the clinicopathologic correlation supported an inflammatory lesion and the patient was followed for 5 years without evidence for the development of systemic lymphoma. The second case, reported by Baum et al., was a 17-yo male with an atypical intravascular CD30+ T-cell proliferation following a traumatic injury. Similarly, the patient had no clinical or laboratory evidence of systemic lymphoma favoring the diagnosis of a reactive pseudolymphoma.

In our case, the intravascular atypical CD30+ T-cell proliferation suggests the histopathologic differential diagnosis of intravascular lymphoma, pseudolymphoma, and a CD30+ lymphoproliferative disorder. The presence of a solitary lesion, the absence of systemic signs or symptoms, the unremarkable laboratory studies, bone marrow biopsy, and PET CT scan, and the lack of a clonal T-cell receptor gene rearrangement favor the diagnosis of a reactive process such as a pseudolymphoma. The patient will be followed closely for the development of any signs or symptoms of systemic lymphoma. This case, in addition to those previously reported in the literature, highlights the importance of thorough clinicopathologic correlation in the evaluation of CD30+ lymphocytic infiltrates.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 15**

Presented by Benjamin Marks, MD, PhD, Emily Keimig, MD, and Joaquin Brieva, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 53 year-old female with a history of systemic lupus erythematous (SLE) was initially seen by the inpatient dermatology service for diffuse discoloration on the legs, The primary medical team had been concerned for an underlying bleeding diathesis. The patient reported that she was diagnosed with SLE five years prior and was started on prednisone and hydroxychloroquine; the discoloration appeared several months after starting both medications. Her rheumatologist advised her that the discoloration was from bruising of the skin due to treatment with prednisone.

PAST MEDICAL HISTORY
Systemic lupus erythematosus, renal transplant

MEDICATIONS
Diltiazem, alprazolam, prednisone, esomeprazole, metoprolol, hydralazine, pravastatin, azelastine, sertraline, hydroxychloroquine, epoetin alfa, cyclosporine, ferrous sulfate, mycophenolate mofetil, folic acid

ALLERGIES
ACE inhibitors

PHYSICAL EXAM
The anterior aspects of the arms and legs had poorly defined blue/gray and brown patches; multiple scars with gray discoloration were also noted. The striae on her upper legs had a gray discoloration. There was no involvement of the fingernails, oral mucosa or conjunctiva.

LABs/IMAGING
Abnormal: Hgb 8.5 gm/dL [11.6-15.4 gm/dL]
Normal: WBC, platelets, CMP

HISTOPATHOLOGY
Dermal fibroplasia and pigment deposits. Special stains showed calcium and melanin deposits and Prussian blue was positive for dermal hemosiderin deposits.

DIAGNOSIS
Hydroxychlorquine-induced hyperpigmentation

TREATMENT AND COURSE
The patient will discuss with her rheumatologist the risk-benefit of continuing the hydroxychloroquine.

DISCUSSION
Antimalarials are first line therapy for systemic lupus erythematosus and other rheumatologic diseases. The reported side effects are diverse, involving multiple organ systems including the gastrointestinal, ocular, haematopoietic, cardiovascular, auditory, mucocutaneous and central nervous systems. Reported adverse cutaneous reactions include pruritus, urticaria, morbilliform eruptions, lichenoid dermatoses, alopecia, hair bleaching, Stevens–Johnson-like syndromes, photosensitivity, and bluish-grey to black discoloration. The exact pathomechanism for the

pigmentation is unknown, however, it has been suggested that it is related to drug binding to melanin and depositing in the skin. The histologic staining pattern is confirmatory, revealing both melanin and hemosiderin deposition.

Localized bluish-grey pigmentation induced by antimalarials was first described among soldiers taking mepacrine for malaria prophylaxis during World War II. Since then, pigmentary disorders from antimalarials have been recognized by the pattern of bluish or grey to black pigment deposition on the shins, face, hard palate, trunk and nail beds. Small studies have suggested that the mean time between the start of treatment and onset of pigmentation ranges between 4 and 70 months, with a mean of 18.5 months. Ten to twenty-five percent of those taking anti-malarial therapy may be affected, and the severity of dyspigmentation is thought to be dose-dependent. Cessation of the medication often improves the discoloration but complete resolution is rare.

We present this case to highlight this well established cutaneous side effect of a common medication, hydroxychloroquine. The dermatologist can play a unique role in identifying the source of dyschromia, particularly when it is overlooked by the prescribing physician. In our case, the patient remained on anti-malarial therapy for several years after the development of leg discoloration which had been attributed to chronic prednisone use. A biopsy may be unnecessary but can be helpful to confirm the source of dyschromia and avoid a more extensive work up for other sources of discoloration such as a bleeding disorder, as was suggested in this case.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 16**

Presented by Lisa Shen, MD, Jennifer Sorrell, MD, Ingrid Polcari, MD, Amy Paller, MD and Anthony J. Mancini, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University and Lurie Children's Hospital

HISTORY OF PRESENT ILLNESS
This 13 year-old female with a history of macrocephaly with Chiari I malformation, developmental delay and sensorineural hearing loss initially presented to the dermatology clinic at age 8 with a four year history of dry pruritic skin. She carried previous diagnoses of eczema and ichthyosis. Over time her skin had become thickened with darker pigmentation involving the face, arms, and trunk. Her pruritus improved steadily and she denied skin irritation. Past treatments included lactic acid 2% in Aquaphor (ineffective) and tazarotene 0.05% cream (poorly tolerated).

PAST MEDICAL HISTORY
Chiari I malformation with no pituitary abnormalities or masses identified
Developmental delay
Sensorineural hearing loss
Early puberty
Ear tubes placed

MEDICATIONS
Tazarotene 0.05% cream to neck and back BID prn, shea butter prn

PHYSICAL EXAM
Weight 77.3kg, Height 157.3cm, BMI 31.24
The patient is well-nourished, in no apparent distress, with coarse facial features and "pseudogigantism". Velvety, hyperpigmented, mamillated and corrugated plaques are distributed throughout the face, neck, chest, back and upper extremities. Her lower extremities are largely spared, except for some very mild pigmentation in the bilateral popliteal regions.

LABs/IMAGING
Abnormal: Total cholesterol 201, triglycerides 116, LDL 103. Endocrine evaluation showed a normal androgen axis but "relatively early puberty" (though not precocious puberty). Pelvic ultrasound showed findings consistent with polycystic ovarian disease. Genetic testing positive for a mutation in exon 19, Glu768Term (an as-of-yet unreported mutation).

Normal: T4, TSH, LH, FSH, DHEA-S, free testosterone, fasting glucose, insulin level, Hgb A1C, random GH, IGF-BP3, IGF-1 level, lipid panel, hepatic function, bone age.

HISTOPATHOLOGY
Right lower back: Sections demonstrate prominent acanthosis and papillomatosis with an undulating epidermis. There is increased basilar pigmentation. The dermis shows a delicate myxoid and edematous stroma with papillomatosis and some telangiectasia.

DIAGNOSIS
Severe diffuse acanthosis nigricans in the setting of FGFR3 receptor mutation

TREATMENT AND COURSE

The patient was advised to continue tazarotene 0.05% cream sparingly as tolerated and Aquaphor daily. Two punch biopsies of the skin were performed to collect keratinocytes to grow in tissue culture. These will ultimately be exposed in vitro to FGFR inhibitors. If effective in inhibiting cellular growth/turnover in vitro, we would consider compounding this topically and applying it to her skin in a localized area.

She was also nominated to attend Camp Discovery, a program sponsored by the American Academy of Dermatology. These week-long summer camps aim to provide an enjoyable and psychologically-supportive environment for children with chronic skin disease.

DISCUSSION

Fibroblast growth factors are transmembrane tyrosine kinase receptors involved in various functions such as mitogenesis, angiogenesis, and wound healing. Fibroblast growth factor 3 (FGFR3) is mapped to chromosome 4p16.3. It has been shown to be a negative regulator of bone growth while conversely causing skin overgrowth in conditions such as linear verrucous epidermal nevi, seborrheic keratoses, dermatosis papulosa nigra, and acanthosis nigricans. FGFR3 mutations have a known association with acanthosis nigricans, typically in the context of Crouzon syndrome or other skeletal dysplasias such as achondroplasia and hypochondrodysplasia. Genetic testing for our patient was recommended given the extent and severity of her acanthosis nigricans, despite the lack of a known skeletal dysplasia. Her testing was positive for a mutation in exon 19, Glu768Term of FGFR3 (an as-of-yet unreported mutation). This is the first stop codon for FGFR3, so mutation presumably leads to a defective FGFR3 product. Interestingly our patient was tall in stature, despite the fact that FGFR3 is generally thought to be a physiological negative regulator of bone growth. Radiographic skeletal survey (performed after we received the positive mutation result) was negative for any evidence of skeletal dysplasias. Of note, Toydemir et al reported a novel mutation in FGFR3 causing camptodactyly, tall stature, and hearing loss (CATSHL) syndrome.

To consider novel therapies for this patient, keratinocyte cultures were initiated from this patient after informed consent. Proliferation studies in the Paller laboratory have shown hyperproliferation of the affected keratinocytes in comparison to normal controls. In addition, 3-dimensional cultures showed abnormal morphology and atypical differentiation. Studies are ongoing to delineate the signaling abnormality, but also to test commercially-available FGFR3 inhibitors for possible reversal of the proliferation and differentiation abnormalities.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE #17**

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HISTORY OF PRESENT ILLNESS
This 33 year-old Caucasian male with a history of recurrent follicular non-Hodgkin's lymphoma s/p matched sibling donor allogeneic stem cell transplant presented in March of 2011 with a two week history of an erythematous, scaly pruritic eruption on his lower extremity. He also noted "white spots" in his axillae, right inner arm, left flank, posterior calf, and left medial instep. Prior to transplant in July 2009, he had received myeloablative conditioning with high-dose busulfan, cyclophosphamide, and etoposide. His post-transplant course was complicated by graft-versus-host disease (GVHD) of the lungs, eyes, and oral mucosa, which developed approximately 7 months post-transplant and one year prior to presentation in our clinic. This was treated with high dose oral corticosteroids and IVIG, with good response. His oral corticosteroids had been weaned off approximately one month prior to presentation. He denied a history of atopy or autoimmune disease, or fevers, chills, nausea, diarrhea, oral ulcers, dry eyes, or joint pain.

PAST MEDICAL HISTORY
Follicular non-Hodgkin's lymphoma s/p allogeneic stem cell transplant

PAST SURGICAL HISTORY
Lymph node biopsy

ALLERGIES
Penicillin, fluconazole, dapsone, sulfa drugs

FAMILY HISTORY
No history of autoimmune disease. Sister from whom he received the stem cell transplant is healthy without any medical problems.

PHYSICAL EXAM.
On the left lower anterior and lateral leg are ill-defined erythematous, scaly thin plaques admixed with depigmented patches. There is significant alopecia and poliosis noted within the patches. On the left axilla, right medial upper arm, left flank, left medial instep are well demarcated depigmented macules and patches

LABs/IMAGING
Abnormal: WBC 3.1 K/uL, Hemoglobin 12.3 g/dL, platelets 73 K/uL
Normal: BMP, LFTs

HISTOPATHOLOGY
L lateral shin: slightly atrophic epidermis with prominent hyperkeratosis and hypergranulosis. There is a superficial band-like lymphohistiocytic infiltrate with squamatization of the basal cell layer and occasional necrotic keratinocytes with satellite lymphocytes. The upper dermis reveals numerous melanin laden macrophages and scattered lymphocytes with slight dermal fibroplasia. MART-1 immunohistochemistry shows no evidence of melanocytes.

L flank: essentially unremarkable epidermis. The dermis shows slight telangiectasia with a mild perivascular and interstitial lymphohistiocytic infiltrate. Scattered melanin laden macrophages were also noted. MART-1 immunohistochemistry shows no evidence of melanocytes.

DIAGNOSIS

Chronic graft-versus-host disease mimicking vitiligo

TREATMENT AND COURSE

The patient was treated with topical triamcinolone 0.1% ointment without improvement. Steroid potency was increased to clobetasol 0.05% ointment for 1 month followed by tacrolimus 0.1% ointment, and NB-UVB phototherapy was recommended as adjunct therapy at his last visit. He decided to pursue this closer to home and has not yet followed-up at NU.

DISCUSSION

Graft-versus-host disease (GVHD) is a multi-organ disease which occurs most commonly in the setting of allogeneic hematopoietic stem cell transplantation (HSCT). GVHD can be divided into two categories, acute GVHD and chronic GVHD, based on organ specific features defined in the 2005 NIH consensus criteria. The pathogenesis of chronic GVHD has not been fully elucidated; however, current research suggests that alloreactive T cells and autoantibodies play a central role. Many chronic GVHD manifestations resemble autoimmune disease, including Sjogren's syndrome and systemic sclerosis, and multiple autoantibodies are often present in patients with chronic GVHD (e.g. anti-neutrophilic antibodies, anti-mitochondrial antibodies, anti-dsDNA antibodies, anti-smooth muscle antibodies) although they may not correlate with specific clinical manifestations. When chronic GVHD mimics an autoimmune disease, it typically does not follow the classic presentation of the disease. For example, although cases of. progressive systemic sclerosis typically begin with Raynauds phenomena and nail fold capillary changes with associated anti-scl70 antibodies, these are most commonly absent in chronic GVHD.

Several autoimmune disorders have been reported post-HSCT including autoimmune thyroid disease, myasthenia gravis, and autoimmune cytopenias. In addition, there are rare case reports of diabetes mellitus, autoimmune hepatitis, anti-phospholipid antibody syndrome, epidermolysis bullosa acquisita, bullous pemphigoid, Addison's disease, vitiligo, and alopecia areata. Hypotheses regarding the pathogenesis of autoimmunity post-HSCT include direct transfer of donor autoimmunity, immunologic dysregulation post-HSCT including impaired central tolerance, and genetic predisposition. In cases where autoimmunity and chronic GVHD have occurred simultaneously, several authors have proposed that the autoimmune syndrome and appearance of autoantibodies may have been triggered by the GVHD or represent a clinical manifestation of the graft-versus-host response.

Vitiligo is a pigmentary disorder resulting in the progressive development of depigmented patches of skin. The most popular hypothesis categorizes vitiligo as an autoimmune disease secondary to melanocyte-specific cytotoxic-T-cell immune destruction of melanocytes. Histologically vitiligo is characterized by an absence of melanocytes in the basal cell layer of lesional skin and vacuolization of keratinocytes in non-lesional adjacent skin and occasionally in lesional skin. As mentioned above, vitiligo and vitiligo-like leukoderma has rarely been reported after HSCT and has almost always been associated with severe cutaneous GVHD. In 2008, Sanli et al. reported 6 cases of generalized vitiligo following HSCT for chronic myeloid leukemia (CML). Five of these cases were associated with severe chronic GVHD and 2 were associated with alopecia areata and acquired ichthyosis. In 2 of the cases, which included one patient who did not have associated GVHD, the donor was affected by vitiligo. The authors concluded in these 6 cases the melanocyte destruction was caused by autoimmune reactions triggered by chronic GVHD in the setting of a genetic predisposition.

In our case we suspect that the patient's dermatologic manifestations represent changes of chronic GVHD mimicking vitiligo due to the histologic findings of GVHD and absence of melanocytes. There was no personal, family, or donor history of vitiligo or autoimmune disease to suggest transfer of donor autoimmunity or a genetic predisposition. However, given the

increasing recognition of de novo autoimmune disease following HSCT, classic vitiligo developing in the setting of chronic GVHD is possible as well. This case highlights an atypical presentation of chronic GVHD, as well as the association between chronic GVHD, HSCT and autoimmune disease.

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