Chicago Dermatological Society

Monthly Educational Conference

Program Information
CME Certification
and
Case Presentations

Wednesday, November 13, 2013

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 Lectures** – *Feinberg A - 3rd Floor* "Molecular Analysis of Dysplastic Nevi and Primary Melanomas" *James G Krueger, MD, PhD* "Seeking the Relevance in Patch Testing" *Emma Guttman, MD, PhD*
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 LECTURES "Psoriasis: Linking Pathogenesis and Therapy" *James G Krueger, MD, PhD* "Atopic Dermatitis: Pathogenic Insights and Emerging Therapeutics" – *Emma Guttman, MD, PhD*
12:00 p.m. - 12:30 p.m.	**Box Lunches & visit with exhibitors** *Feinberg Pavilion Atrium*
12:30 p.m. - 12:45 p.m.	**CDS Business meeting** – *Feinberg A*
12:45 p.m. - 2:30 p.m.	**Case Discussions** – *Feinberg A*
2:30 p.m.	**Meeting adjourns**

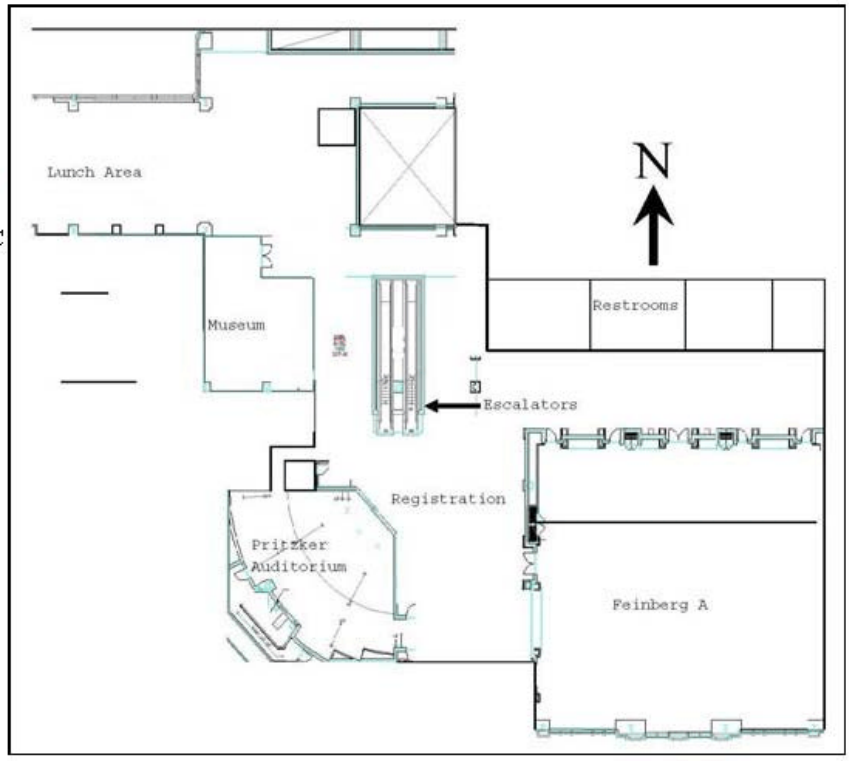
Mark the Date!

Next CDS monthly meeting – SATURDAY, December 14, 2013 at the University of Chicago; Robert Dellavalle, MD, PhD; VA Medical Center; Denver, CO

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

Feinberg Pavilion
3rd Floor layout

To Derm Clinic



Guest Speakers

Delivering the Samuel Bluefarb Lecture

JAMES G. KRUEGER, MD, PHD

Director, Milstein Medical Research Program; Senior Attending Physician, D. Martin Carter Professor in Clinical Investigation, Laboratory of Investigative Dermatology; The Rockefeller University; New York, NY

Dr. Krueger received his bachelor's degree from Princeton University in 1979, his Ph.D. from The Rockefeller University in 1984 and his M.D. from Cornell University Medical College in 1985. He went to Rockefeller as a guest investigator in the Laboratory for Investigative Dermatology, was appointed assistant professor in 1990, associate professor and head of lab in 1995 and professor in 2003. Dr. Krueger has held positions at The Rockefeller University Hospital since 1989. In 2006 he became codirector of the Center for Clinical and Translational Science, established by a Clinical and Translational Science Award from the National Center for Research Resources of the National Institutes of Health. Dr. Krueger was medical director and program director of the General Clinical Research Center from 1996 to 2006 and currently directs the Milstein Medical Research Program, which conducts new clinical studies of the pathogenesis of melanoma and other pigmentory diseases.

EMMA GUTTMAN, MD, PHD

Associate Professor Dermatology; Associate Professor Medicine, Clinical Immunology Mount Sinai Hospital; New York, NY

Dr. Guttman is an Associate Professor of Dermatology & Immunology and Director of the Center for Excellence in Eczema and the Occupational/Contact Dermatitis Clinic and the Director of the Laboratory of Inflammatory Skin Diseases in the Department of Dermatology at the Icahn School of Medicine at Mount Sinai in New York. She earned her MD degree from Sackler School of Medicine at the Tel-Aviv University, and a PhD degree from the Bar-Ilan University Ramat-Gan, Israel. Dr. Guttman completed her first dermatology residency at the Rambam Medical Center/Technion Institute in Haifa. After obtaining her Israeli Board certification in dermatology, she moved to the U.S. to pursue a two-year postdoctoral fellowship at The Rockefeller University in the Laboratory for Investigative Dermatology. She then became board-certified by the American Board of Dermatology after obtaining her second dermatology residency training at the Weill-Cornell Medical College. Dr. Guttman's major clinical focus is in atopic dermatitis/eczema and contact/occupational dermatitis. She has done groundbreaking research and published extensively on inflammatory skin diseases.

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Meeting Series"

November 13, 2013 Chicago, IL

OBTAINING YOUR CERTIFICATE OF CREDIT

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

JOINT SPONSORSHIP STATEMENT

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

GOAL/PURPOSE

To broaden the clinical knowledge of dermatologists.

TARGET AUDIENCE

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

FACULTY

Emma Guttman, MD PhD
Associate Professor Dermatology
Associate Professor Medicine, Clinical Immunology; Mount Sinai Hospital;
New York, NY

James G. Krueger, MD PhD
Director, Milstein Medical Research Program; Senior Attending Physician, D. Martin Carter Professor in Clinical Investigation, Laboratory of Investigative Dermatology; The Rockefeller University;
New York, NY

EDUCATIONAL OBJECTIVES

Upon completion of this series, participants should be able to:

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

2. Describe the manifestation of skin cancers and the efficacy of treatments available to the dermatologist.

3. List the therapeutic options available to the dermatologist for a variety of skin diseases, both medical and surgical, and discuss how new emerging treatments can be successfully

PHYSICIAN ACCREDITATION STATEMENT

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

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

OTHER HEALTHCARE PROFESSIONALS STATEMENT

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

DISCLOSURE STATEMENT

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

Dr. Guttman: Grant/research support - Regeneron; BMS; LEO Pharma; Merck; Janssen.
Consultant - Regeneron; Stiefel/GSK; Celgene; Medimmune.

Dr. Krueger: Grant/research support - Amgen; Pfizer; Lilly; Icon; Glaxo; Kyowa; Novartis; Idera; Merck; Boehringer; Celegene; Paraxel; Provectus.
Consultant - Amgen; Baxter; Biogen Idec; Boehringer; Pfizer; Kineta; Novartis; Janssen; Tekada; Merck; Xenoport

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

Northwestern University
Department of Dermatology
Clinical Faculty

GENERAL DERMATOLOGY
Amy S. Paller, MD, *Chair, Department of Dermatology*
Shatil Amin, MD
Joaquin C. Brieva, MD
Maria L. Colavincenzo, MD
Jonathan A. Cotliar, MD
Kenneth B. Gordon, MD
Emily L. Keimig, MD
Roopal V. Kundu, MD
Anne E. Laumann, MBChB,MRCP(UK)
Mary C. Martini, MD
Stavonnie S.L. Patterson, MD
Monica Rani, MD
Bethanee J. Schlosser, MD, PhD
Jonathan I. Silverberg, MD, PhD, MPH

DERMATOPATHOLOGY
Pedram Gerami, MD
Joan Guitart, MD

DERMATOLOGIC SURGERY
Murad Alam, MD
Simon Yoo, MD

LURIE CHILDREN'S
Anthony J. Mancini, MD, *Head of the Division*
Sarah L. Chamlin, MD
Brandi M. Kenner-Bell, MD
Amy S. Paller, MD
Annette M. Wagner, MD

DERMATOLOGY RESIDENTS

Third Year
Nilanthi Gunawardane, MD (Medicine-Dermatology)
Tracy Donahue, MD
Julia Minocha, MD
Lisa Shen, MD
Jennifer Sorrell, MD

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

First Year
Melanie Clark, MD
Lauren Guggina, MD (Medicine-Dermatology)
Katie Mercy, MD
Lara Rosenbaum, MD

Table of Contents

CHICAGO DERMATOLOGICAL SOCIETY **Case # 1**

Presented by Lisa Shen, MD, Paul Hoesly, BS, Nilanthi Gunawardane, MD, Pedram Yazdan, MD, Bethanee Schlosser, MD, PhD, Joan Guitart, MD, and Joaquin Brieva, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

This 35 year-old Caucasian male was admitted to an outside hospital for evaluation of fatigue, blurry vision, painful purpuric skin lesions, and persistent high fevers. He had previously been treated one month prior to presentation for sinusitis, *Chlamydia pneumoniae* infection, and oral ulcers (responding to valacyclovir and fluconazole). Laboratory tests revealed pancytopenia and acute kidney injury. Ophthalmologic evaluation showed complete vision loss of the left eye due to central retinal artery and vein occlusion as well as bilateral ischemic optic neuritis. Skin biopsies revealed interface and perivascular dermatitis consistent with a hypersensitivity reaction possibly secondary to viral or bacterial infection. An infectious work up including blood cultures and transesophageal echocardiogram were negative.

A systemic vasculitis was suspected, and the patient was treated with methylprednisolone 500mg IV once daily for seven days followed by oral prednisone (1mg/kg/day) without improvement. A vasculitis work up proved to be unrevealing, including normal anti-nuclear antibodies, anti-double stranded DNA antibody, anti-citrullinated protein antibody, rheumatoid factor, anti-neutrophil cytoplasmic antibodies, myeloperoxidase antibodies, complement levels, qualitative cryoglobulins, and negative viral hepatitis titers. Kidney biopsy performed for persistent renal dysfunction showed acute tubular necrosis versus interstitial nephritis, without evidence of glomerulonephritis or small vessel vasculitis. The patient's renal function subsequently normalized. Due to persistent fevers, pancytopenia, skin lesions and vision loss in the setting of a negative vasculitis work up, he was transferred to Northwestern for further evaluation and management.

Upon admission, the patient reported cough, sore throat, and nasal congestion. He reported some weight loss since the illness started, possibly associated with dysphagia. He denied any recent joint pain or swelling, lymphadenopathy, abdominal pain, diarrhea, or urinary symptoms.

PAST MEDICAL HISTORY:

Panic attacks

MEDICATIONS:

Citalopram 10mg daily

FAMILY HISTORY:

No family history of autoimmune disease, hematologic abnormality or malignancy

PHYSICAL EXAM:

HEENT: Hyphema of bilateral eyes. Complete vision loss of the left eye. Tongue and buccal mucosa with scattered white pseudomembranes with no associated erosions or ulcers. No palpable cervical or supraclavicular lymphadenopathy.
Skin: Widely disseminated purpuric, ulcerated and necrotic papules with hemorrhagic crust most densely concentrated on the extremities, buttocks, and acral sites (palms, soles, penis, scrotum). Web spaces between the toes with necrotic ulceration and purulent crust.
Extremities: 2+ edema of bilateral hands and feet

LABS/IMAGING:

Abnormal: WBC 2.6 K/UL (3.5-10.5 K/UL), Hgb 9.6 g/dL (13.0-17.5 g/dL), Plt 94 K/UL (140-390 K/UL), retic count 5.2% (0.1-1.0%), ESR 35 mm/hr (0-20 mm/hr), fibrinogen 198 mg/dL (221-498 mg/dL), ferritin 11,178 ng/mL (24-335 ng/mL), LDH 529 unit/L (<271 unit/L), ALT 63 unit/L (<52 unit/L), AST 68 unit/L (<39 unit/L), triglycerides 335 mg/dL (50-150 mg/dL), vitamin B12 951 pg/mL(180-933 pg/mL), SPEP with abnormal monoclonal IgG kappa band, CSF total protein 114 mg/dL (15-45 mg/dL)

Normal/Negative: BUN, Cr, hypercoagulability panel, haptoglobin, phosphatidylinositol-linked antigens, iron, iron binding capacity, transferrin, PCR of blood for HSV, VZV, and enterovirus; serologies for *Mycoplasma* IgM, HIV, CMV, HBV, HCV, Coxsackie B virus, and treponemes; UPEP, blood bacterial and viral cultures, tissue cultures for bacteria, fungi, and acid fast bacilli, CSF analysis for cell count, cytology, gram stain, bacterial and fungal culture, Coxsackie B virus antibody, and viral PCR (HSV, VZV, EBV, CMV).

Peripheral blood smear: normochromic normocytic anemia. No evidence of a microangiopathic hemolytic process.
Chest radiography**:** heart size and vasculature are normal. The lungs are clear.
CT brain w/o contrast**:** area of hypoattenuation in the left temporal lobe white matter measuring approximately 2.3 cm by 1.2 cm, which could be related to an underlying vasculitis, an ischemic lesion of indeterminate age, or an area of encephalitis.
MRI brain**:** multiple T2/FLAIR hyperintense lesions in the cerebrum and the cerebellum, most of which are associated with enhancement (leptomeningeal more so than parenchymal). There is acute hemorrhage within the left inferior temporal lobe lesion. Findings are concerning for an embolic process (potentially septic emboli), or meningoencephalitis (HSV, VZV, bacterial, fungal disease). Less likely, small vessel vasculitis may show a similar appearance.

HISTOPATHOLOGY:

Sections demonstrate an epidermis with a broad area of central necrosis. Single apoptotic keratinocytes are identified in the adjacent epidermis. An interface inflammatory infiltrate is identified. Within the necrotic areas, there are numerous bands and early neutrophils likely an inflammatory response to the necrotic tissue. Atypical lymphocytes were not identified. Immunohistochemistry revealed many CD3-positive lymphocytes with a mixture of CD4 and CD8 lymphocytes near the epidermis. The CD5 is dim. There is some TIA-1 positivity in the lymphocytic infiltrate. The CD56, Gamma M1, CD1a and EBER are negative. Myeloperoxidase labels many myeloid cells near the area of epidermal necrosis. Special stains (DPAS, Gram and acid fast bacilli) were negative for microorganisms.

DIAGNOSIS:

Febrile Ulceronecrotic Mucha Habermann Disease (FUMHD)

TREATMENT AND COURSE:

The patient was treated with IV methylprednisolone 500mg once daily for five days and subsequently transitioned to oral prednisone 60mg daily. His cutaneous lesions gradually improved during the hospital course without the appearance of new lesions. He remained afebrile during the course of the hospitalization, and his blood counts gradually normalized. Vision in the right eye returned to baseline, but he continued to have complete blindness of the left eye. This visual deficit persisted at a 3-week outpatient follow-up visit despite continued high-dose oral corticosteroids.

DISCUSSION:

Febrile ulceronecrotic Mucha-Habermann disease (FUMHD) was first described by Degos in 1966 as a severe variant of pityriasis lichenoides et varioliformis acuta (PLEVA). It is more common in children and young adults, with the majority of cases occurring in individuals younger than 30 years of age. It is thought to be a cutaneous hypersensitivity response to numerous implicated infectious agents, though the exact pathogenesis is unknown.

Systemic symptoms are a prominent feature distinguishing FUMHD from PLEVA. Persistent fevers, pancytopenia, and diffuse ulceronecrotic skin lesions, as occurred in our patient, are common. The skin lesions can also affect oral, perineal, and conjunctival mucosa, as well as palms and soles. Other systemic manifestations may include lymphadenopathy, myalgia, arthralgia, interstitial pneumonitis, gastrointestinal symptoms, lymphocytic myocarditis, megaloblastic anemia, and disseminated intravascular coagulation. CNS involvement is rare, with only two previously reported cases. Ophthalmologic manifestations have not previously been reported. In one case of CNS involvement described by Rosman, biopsy of the brain showed necrotizing vasculitis in the right frontal lobe. Our patient likely suffered a similar inflammatory process in the vasculature supplying the optic nerves and retina, resulting in an ischemic optic neuropathy. The mortality rate of FUMHD is approximately 20%, with reported fatalities attributed to thromboembolic events, pneumonia, cardiac arrest, sepsis, and hypovolemic shock.

Evaluating treatment strategies for FUMHD is difficult because of the limited number of cases reported in the literature. Systemic corticosteroids are often used as first-line therapy, although there are several cases that suggest the use of methotrexate alone or in combination with a corticosteroid to be more effective in stopping disease progression. Cyclosporine, antibiotics, and ultraviolet phototherapy have also been employed with some success. The use of cyclophosphamide in conjunction with systemic corticosteroids in a single patient with CNS involvement has been reported to be effective in improving neurologic symptoms.

This case highlights the potential for an irreversible ischemic optic neuropathy in patients with FUMHD. Urgent ophthalmologic and neurologic consultation should be considered for patients with PLEVA who develop ocular symptoms.

References:

1) Degos R, Duperrat B, Daniel F. Le parapsoriasis ulceronecrotique hyperthermique. Ann Dermatol Venereol (Paris) 1966;93:481-496.

2) López-Estebaranz JL, Vanaclocha F, Gil R, García B, Iglesias L. Febrile ulceronecrotic Mucha-Habermann disease. J Am Acad Dermatol. 1993 Nov;29(5 Pt 2):903-6.

3) Meziane L, Caudron A, Dhaille F, Jourdan M, Dadban A, Lok C, Chaby G. Febrile ulceronecrotic Mucha-Habermann disease: treatment with infliximab and intravenous immunoglobulins and review of the literature. Dermatology. 2012;225:344-348.

4) Rosman I, Liang L, Patil S, Bayliss S, White A. Febrile ulceronecrotic Mucha-Habermann disease with central nervous system vasculitis. Pediatric Dermatology 2013;30(1):90-93.

5) Sotiriou E, Patsatsi A, Tsorova C, Lazaridou E, Sotiriadis D. Febrile ulceronecrotic Mucha-Habermann disease: a case report and review of the literature. Acta Derm Venerol. 2008;88(4):350-5.

6) Suarez J, Lopez B, Villalba R, Perera A. Febrile ulceronecrotic Mucha-Habermann disease: a case report and review of the literature. Dermatology. 1996;192:277-9.

7) Tsianakas and P.H. Hoeger. Transition of pitryriasis lichenoides et varioliformis acuta to febrile ulceronecrotic Mucha-Habermann disease is associated with elevated serum tumor necrosis factor alpha. British Journal of Dermatology 2005;152:794-799.

CHICAGO DERMATOLOGICAL SOCIETY **Case #2**

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

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **Case #3**

Presented by Melanie Clark, MD, Bethanee Schlosser, MD, PhD, Maria Colavincenzo, MD, and Roopal V. Kundu, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

CASE A

HISTORY OF PRESENT ILLNESS

This 59 year-old Caucasian man presented for evaluation of a non-healing, painful, enlarging ulcer on his right thigh for 1 year. Previous treatment at a wound care center included local wound care, oral antibiotics, four weeks of intravenous antibiotics, wound vacuum, two surgical debridements with Graftjacket ® placement, and one surgical debridement with Apligraf ® placement. Despite these therapies, his ulcer continued to enlarge.

PAST MEDICAL HISTORY:

Type II diabetes mellitus
No history of inflammatory bowel disease, autoimmune disease, or malignancy

MEDICATIONS:

Hydrocodone/acetaminophen, metformin, silver sulfadiazene strips

FAMILY HISTORY:

No history of inflammatory bowel disease, autoimmune disease, or malignancy

PHYSICAL EXAM:

The right mid thigh was notable for a 16 cm x 16 cm ulcer with undermined, rolled borders with erythema of the surrounding skin. The ulcer contained a central area of beefy red granulation tissue surrounded by contiguous ulcers separated by thin pink septae with scalloped borders and an overlying yellow fibrinous exudate.

LABS/IMAGING:

Abnormal: WBC 14.0 K/UL (3.5-10.5 K/UL), Hgb 12.8 (13.0-17.5 g/dL), Plt 432 K/UL (140-390 K/UL), iron 17 ug/dL (50-212 ug/dL), transferrin 180 mg/dL (203-362 mg/dL), TIBC 204 ug/dL (250-450 ug/dL), transferrin saturation 8% (20-50%), SPEP/IFE with abnormal monoclonal IgG kappa band, ESR 51 mm/hr (0-20 mm/hr), CRP 35.7 mg/dL (0-0.5 mg/dL)

Wound culture: few *Staphylococcus aureus*, few *Pseudomonas aeruginosa*
MRI right femur: subcutaneous defect right lateral thigh without involvement of deeper tissues
Colonoscopy: stricture of terminal ileum; erosive/ulcerative colitis of the cecum and ileocecal valve; right colon unremarkable; left colon with an erosion with a benign lymphoid aggregate

Normal/Negative:

LFTs, ferritin, vitamin B12, folate, reticulocyte count, CCP, G6PD, UPEP, Hep B, Hep C, HIV, QuantiFERON®-TB gold, C3 & C4, ANA, RNP, p-ANCA, c-ANCA

HISTOPATHOLOGY:

Ulcer, granulation tissue, and dermal and subcutaneous suppurative inflammation with focal vasculitis

DIAGNOSIS:
Pyoderma gangrenosum

TREATMENT AND COURSE:
The patient was admitted to Northwestern Memorial Hospital with plans to start therapy with prednisone and infliximab. Due to wound culture growth of many *Pseudomonas aeruginosa* on admission, prednisone therapy was deferred, and he was given an initial dose of infliximab (500mg) and started on IV vancomycin and piperacillin/tazobactam. He was discharged on hospital day #5 with a PICC line and two-week course of cefepime and vancomycin. Since discharge on July 26, 2013, he has been applying acetic acid washes, Mepilex®, and mupirocin to the base of the ulcer twice daily and applying clobetasol 0.05% ointment twice daily to the ulcer edges. He received subsequent infliximab (500mg) infusions at weeks 2, 6, and 14. His ulcer has been regranulating and currently measures 11 cm x 13 cm. He has an appointment to see hematology-oncology for evaluation of his IgG monoclonal gammopathy.

CASE B
HISTORY OF PRESENT ILLNESS
This 32 year-old Caucasian female presented in January 2012 for chronic vulvar ulcerations with associated vulvar pain, bleeding, yellow mucoid discharge, and itching since 2008. The patient was previously diagnosed with plasma cell vulvitis. She was treated with oral prednisone in 2009 with significant improvement and also reported mild improvement with previous treatment with topical halobetasol, intralesional steroids, and Instant Ocean. In 2010, she underwent ulcer excision of the left and right vaginal vestibule with failure to heal and recurrence of ulcers. The vulvar ulcers caused significant functional impairment with dyspareunia.

PAST MEDICAL HISTORY
Asthma, hemorrhoids, herpes labialis, mild GERD
No history of abnormal Papanicolaou smears
No history of inflammatory bowel disease, autoimmune disease, or malignancy

MEDICATIONS:
Halobetasol ointment 0.05%

FAMILY HISTORY:
No history of inflammatory bowel disease, autoimmune disease, or malignancy

PHYSICAL EXAM
The patient's vulvar exam was notable for coalescing friable exophytic erythematous (red to violaceous) papules with ragged superficial ulcers, and active bleeding extending from 2 to 11 o'clock of the vaginal introitus (clockwise). The right lateral edge of the lesion had a violaceous hue and slightly rolled, edematous borders. Speculum examination was notable for one linear ragged ulcer extending 1.5-2 cm past the hymen posteriorly at 7 o'clock. Perianal skin was notable for multiple hemorrhoidal tags with no fissure or ulcer.

LABS/IMAGING:
Abnormal: ANA 1:40 – 1:80

Normal/Negative:
CBC, LFTs, CCP, dsDNA, SSA Ab, SSB Ab, Sm Ab, RNP Ab, c-ANCA, p-ANCA, lupus anticoagulant, G6PD, RPR, Hep B, Hep C, HIV, Quanti-FERON® gold, SPEP, UPEP

Colonoscopy: perianal skin tag, biopsies of ileum and colon normal, no evidence of inflammatory bowel disease

HISTOPATHOLOGY
Chronic suppurative and granulomatous mucositis with dense plasma cell infiltrates. Warthin-Starry, GMS and AFB were negative for microorganisms. The kappa and lambda immunostain showed a polyclonal process.

DIAGNOSIS:
Pyoderma gangrenosum

TREATMENT AND COURSE
The patient was started on prednisone 60 mg (1mg/kg) daily for four weeks with near-complete healing of ulcer. She was tapered by 5 mg every two weeks and had recurrence of superficial vulvovaginal ulcer on prednisone 30 mg. She was subsequently started on mycophenolate mofetil 500 mg BID and continued on prednisone 30 mg daily. Her steroid course was complicated by vulvovaginal candidiasis and acne vulgaris. She was tapered off of prednisone by 5 mg every 2 weeks with an increase in her mycophenolate mofetil dose to 1000 mg BID. Her ulcers were initially stable on mycophenolate mofetil 1000 mg BID but eventually began to enlarge, and her dose was increased to 1500 mg BID. Halobetasol 0.05% ointment once daily was also restarted at this time. She has continued to have two small superficial stable ulcers on this treatment regimen since it was started in November 2012 but no longer has vulvar pain or bleeding and is now able to have sexual intercourse without pain or discomfort. She has not required pelvic floor physical therapy or vaginal dilators.

DISCUSSION
Pyoderma gangrenosum (PG) is an uncommon neutrophilic dermatosis with an unknown etiology. It is characterized by chronic, painful, recurrent ulcerations. The classic PG ulcer usually starts as a tender papule with surrounding erythema that extends centrifugally over time to form an ulcer with an erythematous to violaceous rolled, undermined border. PG is most commonly found on the lower extremities but may be seen at any cutaneous or mucocutaneous site on the body. Pathergy both initiates and exacerbates ulcers caused by PG. Lesions are often worsened significantly by surgical debridement that is performed with curative intent when ulcer etiology is unknown or misdiagnosed, as demonstrated in both of the above patients.

Histopathology of PG is variable and often nonspecific. In advanced disease, there is often a dense neutrophilic infiltrate that is folliculocentric and may be folliculodestructive. Varying levels of other inflammatory cells such as neutrophils, eosinophils, and mast cells may be present. Vasculitis may be present but likely represents change secondary to inflammation rather than the inciting event. Because of its variable presentation, a diagnosis of PG should be made based on clinical history and histopathologic correlation.

There is no gold standard treatment algorithm for PG, and treatment is generally targeted at reducing inflammation in order to promote healing. Topical, intralesional, and systemic corticosteroids are often first-line. Systemic steroid-sparing agents are commonly used in conjunction with corticosteroids and may be the preferred choice for patients requiring long-term therapy. Options for systemic steroid-sparing agents include systemic calcineurin inhibitors (cyclosporine), antimetabolites (azathioprine, methotrexate, mycophenolate mofetil), and TNF-alpha inhibitors (infliximab, adalimumab, etanercept). Approximately 50% of patients with PG have an associated hematologic disorder, autoimmune disease, or inflammatory bowel disease, and it is imperative to conduct appropriate screening tests for these conditions. In patients with

concurrent systemic disease such as rheumatoid arthritis, monoclonal gammopathy, or Crohn's disease, treatment is targeted at controlling the underlying disease process.

The TNF-alpha inhibitor infliximab opposes TNF-alpha, a pro-inflammatory cytokine. Infliximab is pregnancy category B but is not widely used in pregnancy due to its relative novelty as a therapeutic agent and concerns about safety. Infliximab is FDA-approved for the treatment of inflammatory bowel disease (IBD) and has been used to treat patients with concurrent PG and IBD with reasonable success. However, infliximab also appears to be a valuable therapy for non-IBD associated PG. Anti-TNF therapies have been used off-label for a multitude of dermatologic diseases including PG, sarcoidosis, hidradenitis suppurativa, scleroderma, pityriasis rubra pilaris, necrobiosis lipoidica and panniculitis. A recent case series of six patients with PG (three with concurrent IBD) treated with infliximab 5 mg/kg at weeks 0, 2, 6 and every 8 weeks thereafter demonstrated complete resolution of ulcers at a mean of 10.2 months after a mean of 8.2 infusions. In a randomized, placebo-controlled trial of 30 patients with PG, patients who received a single or multiple doses of 5 mg/kg infliximab had significantly better outcomes than the placebo group. Furthermore, there were no significant differences in response to infliximab demonstrated between patients with and without IBD.

Mycophenolate mofetil (MMF) is an antimetabolite that selectively inhibits the purine salvage pathway in T and B cells and is an immunosuppressant that is FDA-approved for anti-rejection therapy in organ transplant patients. MMF's target dose is 2-3 g/day. MMF is pregnancy category D, and in 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) for mycophenolate-containing medications to prevent unplanned pregnancies in patients using MMF and to minimize fetal exposure to MMF. The approved REMS included training for health care professionals, a medication guide for patients, and a pregnancy registry for patients who become pregnant on MMF. When MMF is prescribed off-label as a therapy for PG, its healing-promoting effects are thought to be mediated by decreased levels of immunoglobulins and inflammation. In a recent retrospective analysis of 26 patients with PG being treated with prednisolone and MMF, almost 85% showed clinical improvement during treatment with MMF. Approximately half of the study participants were receiving concurrent therapy with other steroid-sparing immunomodulators, and two-thirds had no underlying systemic disease. In another retrospective study of seven patients with PG treated with MMF monotherapy, 6 of 7 patients showed some reduction in ulcer size and 4 of 7 healed completely.

Although large randomized controlled trials are lacking, systemic steroid-sparing immunomodulators such as infliximab and mycophenolate mofetil show promise as both monotherapy and in multi-agent therapy regimens for selected patients with PG.

References:

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CHICAGO DERMATOLOGICAL SOCIETY **CASE #4**

Presented by Luzheng Lisa Liu, MD PhD and Roopal V. Kundu, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 44 year-old Hispanic woman presented with a five-year history of progressive vitiligo involving large areas of the face, neck, trunk and extremities. Given the extensive involvement, the patient requested depigmentation therapy. Prior to her initial visit at Northwestern, she received a four-month treatment course of hydroquinone 4% cream without perceivable benefit.

PAST MEDICAL HISTORY
Hypertension

MEDICATIONS
Atenolol, lisinopril/hydrochlorothiazide

ALLERGIES
No known drug allergy

FAMILY HISTORY
No family history of vitiligo, father and brother with thyroid disease, both parents with diabetes mellitus.

SOCIAL HISTORY
Married with two children, works as a child care provider, denies tobacco, alcohol or drug use.

PHYSICAL EXAM
The patient's cutaneous exam was notable for extensive depigmented patches on the face, hands, and forearms extending up towards the upper arms. The dorsal hands and all fingers were nearly completely depigmented. Numerous depigmented macules coalescing into small patches were present on the trunk and legs. Approximately 30% body surface area was involved.

DIAGNOSIS
Vitiligo

TREATMENT AND COURSE
Depigmentation with monobenzone (monobenzyl ether of hydroquinone) was discussed at her initial visit. Given the potential psychosocial implications, psychologic counseling was initiated prior to therapy. Monobenzone 20% cream was started twice a day for one week to one test area on the arm and was subsequently applied to the residual pigmented areas of the face and neck twice a day in December 2011. Due to mild irritation and erythema on the face, treatment frequency for facial skin was reduced to once daily. Marked clinical response was observed at her follow-up visit in April 2012, with near complete depigmentation of the face and neck. She continued to develop depigmented areas in both monobenzone-exposed and unexposed skin with ongoing treatment and strict sun protection. The patient was very pleased with the results. Monthly psychotherapy sessions were held concomitantly to support treatment compliance, provide counseling on social ramifications of appearance changes, help to manage changes in self and cultural/ethnic identity, as well as impact on marital relations.

DISCUSSION

Monobenzone, the monobenzyl ether of hydroquinone, is the most potent depigmenting agent currently available. Although well-tolerated with few side-effects (irritant dermatitis or consort vitiligo via body contact), its use is limited due to the potent, systemic and irreversible nature of the drug. This case presents an example of when timely and aggressive treatment with monobenzone is warranted, demonstrating excellent clinical response in a patient with severe vitiligo.

In 1939, Oliver et al. discovered that monobenzone, present in the rubber gloves of leather tannery workers, induced progressive skin depigmentation that was indistinguishable from vitiligo. Depigmentation was noted in both exposed and non-exposed sites, suggesting a systemic effect. However, little wass understood about the mechanisms of monobenzone-mediated depigmentation until very recently. Using both *in vitro* and *in vivo* approaches, van den Boorn et al showed that monobenzone, when applied to pigmented skin, inhibits melanogenesis by directly inactivating tyrosinase. It also induces reactive oxygen species formation in melanocytes, thus initiating autophagy pathways and tyrosinase ubiquitination, leading to melanosome destruction. In addition, monobenzone binds to tyrosinase and forms quinone-haptens that are excreted in the exosomes. The quinone-haptens act as neoantigens, while exosomes induce robust innate inflammatory responses and stimulates antigen processing for both the MHC class I and II routes. This leads to the development of melanocyte-specific systemic T cell responses and circulating antibody formation that recognize both haptenated and native melanocyte antigens released from lysed monobenzone-exposed cells and exosomes. This explains why non-monobenzone exposed melanocytes can be progressively destroyed, leading to progressive depigmentation in non-exposed skin. The immune-stimulatory properties of monobenzone make it an attractive adjunct agent for melanoma immunotherapy. Preliminary studies have shown that monobenzone-exposed melanoma cells, in contrast to unexposed melanoma cells, were highly immunogenic and able to induce a strong pigment cell-specific CD8+ T cell response in healthy human donors.

Finally, we would also like to highlight the importance of adjunct psychologic support during depigmentation therapy. The change in appearance caused by vitiligo itself can significantly affect a person's emotional and psychological well-being. Further permanent loss of native skin color with depigmentation therapy may create additional difficulty in family, professional and social situations, as well as adjustment issues with self, cultural, and ethnic identity. This warrants ongoing psychological support to optimize compliance and improve treatment success, which is ultimately measured by improvement in patient quality of life.

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Fast Break A

Presented by Julia Minocha, MD, Joaquin Brieva, MD, Monica Rani, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

This is a 38 year-old female who presents with a one-week history of erythematous, indurated, painful plaques over the flanks and abdomen with associated fevers. Approximately 3 months prior, the patient underwent abdominoplasty, breast augmentation, liposuction, and fat injection to the buttocks in the Dominican Republic.

What organism should be suspected in this infection?

CHICAGO DERMATOLOGICAL SOCIETY **Case #5**

Presented by Katherine Mercy, MD and Anthony J. Mancini, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 8 year-old Hispanic female presented with multiple congenital anomalies, including alopecia and recurrent scalp erosions present since birth. At the same time, she experienced xerosis, pigmentary changes, and intermittent desquamation, but no bullae or ulcerations. The patient was initially diagnosed with epidermolysis bullosa in Mexico where she was born. In addition, she had a history of a congenital cleft lip and palate, which were partly repaired through two surgical procedures in Mexico. She reported decreased sweat production, which was most pronounced during periods of fever and physical activity. She was born with malformations of the feet, but she has been able to ambulate with the assistance of inserts and wide shoes.

PAST MEDICAL HISTORY:
Unilateral right cleft lip and palate, alopecia, bilateral entropion and corneal scarring, hypoplastic auditory canals and otorrhea, dental caries, hypohidrosis, left vesicoureteral reflux and recurrent urinary tract infections, malformations of the feet, speech delay

MEDICATIONS:
Trimethoprim-sulfamethoxazole, hyaluronic acid eye drops, SPF 50+ sunscreen

FAMILY HISTORY:
No family history of genetic disorders

PHYSICAL EXAM:
Scarring alopecia and minimal hair growth in the ophiasis pattern were noted on the scalp. Facial dysmorphism was present, with a partially repaired cleft lip/palate and hypoplastic auditory canals. Eye examination revealed scleral injection and photophobia to the examination room lights. Upper extremities and trunk demonstrated multiple hyper- and hypopigmented patches and diffuse xerosis. Examination of the dorsal hands revealed atrophy, linear scars, nail hypoplasia and pterygium inversum unguis to full pterygium in some nails. Split-foot malformation with absent digits was also noted.

LABS/IMAGING:
Abnormal: Voiding cysto-urethrogram with Grade 1 left vesicoureteral reflux

DIAGNOSIS:
Ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) syndrome

TREATMENT AND COURSE:
Counseling was provided about vigorous sun protection and strategies to avoid overheating. The patient was referred to Plastic Surgery/Cleft Clinic, Orthopedic Surgery, Dentistry, Audiology, Urology, Ophthalmology and Genetics. Information was given about the National Foundation for Ectodermal Dysplasia.

DISCUSSION:
Initially described by Rudiger and colleagues in 1970, EEC is a variant of ectodermal dysplasia characterized by ectrodactyly of the hands and feet, ectodermal dysplasia, and facial clefting. EEC is a rare entity, with almost 200 cases reported in the literature. Heterozygous mutations of

the *p63* gene, located on chromosome 3p27, account for the majority of cases of EEC. These missense mutations in the p63 DNA-binding domain result in altered keratinocyte proliferation and differentiation. EEC is normally inherited in an autosomal dominant fashion, though sporadic cases have been identified. The AEC syndrome, limb-mammary syndrome, ADULT (acro-dermato-ungual-lacrimal-tooth) syndrome, and non-syndromic split hand-split foot mutation have also been linked to *p63* mutations. However, distinct heterozygous mutations with a varying effect on p63 function account for the different phenotypes seen in these syndromes.

Studies among and between families with EEC demonstrate variability in expression of phenotypes of affected individuals. Variations in distal limb anomalies range from simple syndactyly to the tetramelic cleft hand and foot (lobster claw) defect. A review of 24 cases by Buss et al shows that hair and teeth are affected in all individuals. In contrast, nail dystrophy and hypohidrosis are seen in 79% and 13% of cases, respectively. Skin involvement most commonly appears as xerosis and scaling of the neck and extremities, along with fissures of the interdigital webbed spaces. Moreover, individuals may present with a range of unilateral to bilateral clefting of the lip and/or hard palate.

In addition to the classic features of ectrodactyly, ectodermal dysplasia, and clefting, additional malformations may be seen in the EEC syndrome. Urinary tract anomalies are reported in 8-52% of patients with EEC and include structural defects and dysplasia of the bladder epithelium. In some reports, the acronym EECUT (UT standing for urinary tract) accounts for the common occurrence of urinary tract anomalies seen in these individuals. Common ocular anomalies include meibomian gland defects, impaired lacrimal drainage, and progressive limbal cell deficiency resulting in visual impairment. Individuals may also experience hearing loss as a result of sensorinerual or conductive defects (cerumen impaction and recurrent otitis media). Speech delay may result from facial clefting and any associated otologic anomalies. In one review, cognitive delay is estimated to occur in 7% of affected individuals. Treatment of patients with EEC is symptomatic and includes management of its multiple comorbidities.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #6**

Presented by Pedram Yazdan, MD and Pedram Gerami, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 51 year-old male presented with a history of dysplastic nevus syndrome and 6 primary cutaneous malignant melanomas:
-2013: right upper arm, melanoma in situ
-2010: left shoulder, malignant melanoma, superficial spreading type, Breslow depth 0.65 mm
-2009: anterior chest, malignant melanoma, superficial spreading type, Breslow depth 0.45 mm
-2005: left mid-chest, malignant melanoma, superficial spreading type, Breslow depth 1.4 mm
-2003: right nose, malignant melanoma, nodular type, Breslow depth 3.2 mm
-1998: right upper back, malignant melanoma, superficial spreading, Breslow depth 0.36 mm
-Numerous epithelioid Spitz tumors
In 2012, a changing lesion was noted on the left upper back prompting biopsy.

FAMILY HISTORY:
No history of melanoma. Has 5 siblings, 2 with atypical nevi. He has a16 year-old son with a history of dysplastic nevi and epithelioid Spitz tumor. Mother died of lung cancer.

PHYSICAL EXAM:
Trunk, legs and arms with >100 nevi. Left upper back with a 8mm x 5mm erythematous-pink pedunculated papule with a focus of new reticulation at periphery and new telangiectasia.

LABS/IMAGING:
Abnormal: tumor tissue from the left upper back biopsy revealed loss of nuclear staining of BAP1

Normal/Negative: CBC w/differential, BMP, LFTs, LDH, Chest X-ray, CT of chest/abdomen/pelvis, PET scan, ocular exam

HISTOPATHOLOGY:
There was a biphasic compound melanocytic lesion. Centrally, there was a dense sheet-like proliferation of large atypical epithelioid melanocytes with spitzoid features, including cells with abundant pink-glassy cytoplasm, pleomorphic nuclei with course chromatin, prominent nucleoli and pseudo-nuclear inclusions. A second melanocytic component was also noted consisting of nests of small and banal appearing nevomelanocytes. Ki-67 (proliferative marker) shows virtually no proliferative activity within the atypical dermal component. BAP1 staining by immunohistochemistry showed normal diffuse nuclear expression of BAP1 in the nests of conventional nevus cells while the atypical epithelioid nevus component showed loss of BAP1 nuclear staining and a clumped perinuclear staining pattern.

DIAGNOSIS:
Familial Uveal Melanoma Syndrome with germline mutation in *Bap1* resulting in multiple melanomas and *Bap1*-related epithelioid Spitz tumors

TREATMENT AND COURSE:
The patient underwent wide local excisions for his primary melanomas. Lymph node biopsies revealed a focus of micrometastatic melanoma found in one axillary sentinel lymph node in 2005. In 2006, he was initiated on high-dose interferon for 2 months but was discontinued due to intolerable adverse effects. Evaluation of saliva and tumor tissue showed evidence of a germline mutation in *Bap1*. The remaining family members are currently being evaluated.

DISCUSSION:

BRCA1-associated protein 1 (BAP1) represents a recently identified tumor suppressor protein that is believed to mediate its effects through chromatin modulation, transcriptional regulation, and possibly via the ubiquitin-proteasome system and the DNA damage response pathway. Mutations in *BAP1* that result in either protein truncation or loss of function in the ubiquitin carboxyl-terminal hydrolase domain are frequently observed in metastatic uveal melanomas. Germline mutations in *BAP1* have been found to predispose some carriers to cutaneous melanomas, mesotheliomas, atypical cutaneous melanocytic lesions, clear cell renal cell carcinoma, lung adenocarcinomas and uveal melanomas. However, the complete tumor spectrum associated with germline *BAP1* mutations is not yet known. Tumors result from loss of heterozygosity either by a second mutation or deletion, or from epigenetic modification.

Cutaneous melanocytic lesions in patients carrying the *BAP1* germline mutation have been reported to present clinically as skin-colored papules or nodules. Histopathology consists commonly of a combined melanocytic neoplasm often with a conventional melanocytic nevus component and a second component of epithelioid melanocytes with spitzoid cytomorphology but lacking other features of Spitz nevi including epidermal hyperplasia, Kamino bodies, clefting or spindle-shaped melanocytes. Wiesner et al. recently described an autosomal dominant syndrome in which patients develop many combined melanocytic neoplasms consisting of conventional nevus cells and a second population of an atypical epithelioid Spitz tumor component. Subsequently, the same investigators described sporadic epithelioid Spitz tumors with histopathologic findings similar to the melanocytic tumors associated with the familial syndrome.

Awareness of these tumors will help to identify patients with a high likelihood of harboring germline or somatic *BAP1* mutations. Consideration should be given to testing for *BAP1* mutations in epithelioid atypical Spitz tumors and uveal melanomas, or when other *BAP1*-associated tumors occur in individual patients. Lesional skin biopsies may be screened for *BAP1* mutations/loss/inactivation by immunohistochemistry (IHC) (demonstrating loss of nuclear staining in tumor cells). Confirmatory sequencing may be considered in tumors that exhibit *BAP1* loss by IHC and in those with equivocal IHC results. Identification of a *BAP1* mutation raises the possibility of a *BAP1* germline mutation and may warrant consideration of genetic counseling and further testing of the patient and their family. To date, most reports suggest a favorable prognosis for *BAP1*-mutated epithelioid Spitz tumors, including our own patient. If the individual is found to be a mutation carrier, they should be closely monitored clinically. Regularly scheduled dermatological, ophthalmological, and pulmonary evaluations should be considered to enhance the possibility of early intervention.

Importantly our patient and his family have had no evidence of ocular melanomas but have had many cutaneous melanomas. Previous reports of patients with germline mutations in *BAP1*have not described patients with multiple cutaneous melanomas. We hypothesize that the presence of the *BAP1* germline mutation in the presence of a patient with a dysplastic nevus phenotype is the source of the multiple cutaneous melanomas in our patient.

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Fast Break B

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

What is your diagnosis?

CHICAGO DERMATOLOGICAL SOCIETY **Case #7**

Presented by Jennifer Sorrell, MD and Sarah Chamlin, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University and Division of Dermatology, Ann and Robert H. Lurie Children's Hospital of Chicago

CASE A

HISTORY OF PRESENT ILLNESS

This 31-month-old female presented to the Lurie Children's Vascular Lesion Clinic with a large capillary malformation involving the left cheek and chin. This lesion had been progressively increasing in elevation and redness for the preceding few months and was noted to feel warmer than the surrounding skin. In addition, she was noted to have acquired several smaller capillary malformations on the forehead, trunk and extremities.

Of note, an MRI was performed at 19 months of age which revealed a CNS vascular malformation involving the vein of Galen. She subsequently underwent embolization of the high flow arteriovenous fistula between the distal left posterior cerebral artery and the dilated basal vein of Rosenthal at 33 months of age.

She also complained of weakness in her left leg, resulting in difficulty with activities such as climbing stairs or jumping. Neurologic evaluation demonstrated unilaterally increased tonicity. The patient denied headaches or other CNS complaints.

PAST MEDICAL HISTORY:

Born at full term via caesarean section with vacuum assist, no NICU stay

MEDICATIONS:

None

FAMILY HISTORY:

Mother and four-year-old sister both with *RASA1* mutations and history of "hemangiomas" (though lesions clinically consistent with capillary malformations on our exam)
Maternal grandmother with facial birthmarks

PHYSICAL EXAM:

There is an erythematous large vascular patch on the left medial cheek associated with increased fullness and warmth of the affected area. There is no palpable pulsation noted. Vascular telangiectatic macules and patches are appreciated on the left jaw, bilateral arms, chest and lower extremities (many with a rim of pallor).

LABS/IMAGING:

Abnormal:

MRI/MRA brain and spine: Treated left paramedian occipital vascular lesion. Apparent occlusion of a feeding left posterior cerebral artery branch and occlusion/thrombosis of the venous varix. There remains a signal abnormality along the periphery of the vascular lesion, and there is persistent enlargement of the adjacent left vein of Rosenthal. Residual fistula cannot be excluded.
Genetic testing: deletion in *RASA1* gene but no missense mutation (normal sequencing).

CASE B

HISTORY OF PRESENT ILLNESS

This 17-month-old male presented to the Lurie Children's dermatology clinic with multiple vascular patches. He had three vascular patches present at birth on the back, right antecubital fossa and right knee. Over several months, he developed approximately 15 new vascular patches. He was otherwise thriving and achieving his developmental milestones.

He had no gross gastrointestinal bleeding but had three stool guaiacs positive for heme. He also had a vascular ring of his airway with stridor noted during infancy which continues to improve.

PAST MEDICAL HISTORY:

Atopic dermatitis

MEDICATIONS:

Prednicarbate 0.1% emollient cream and oral hydroxyzine

FAMILY HISTORY:

No family history of vascular lesions

PHYSICAL EXAM:

The patient's cutaneous exam was notable for more than 15 vascular patches and macules, with the two largest vascular plaques located on the right shoulder and right arm. Within the vascular patches, there are prominent vessels and minimal atrophy noted.

LABS/IMAGING:

Abnormal:

Genetic testing: substitution mutation in *RASA1* gene (c.1870C>T)

DIAGNOSIS:

Capillary malformation- arteriovenous malformation (CM-AVM) syndrome associated with mutation in the *RASA1* gene

DISCUSSION:

Capillary malformation-arteriovenous malformation syndrome is characterized clinically by the presence of multiple capillary malformations (CMs) with or without arteriovenous malformations (AVMs) and arteriovenous fistulas (AVFs). CMs in this condition are usually multifocal, <1–3 cm in diameter and round or oval pink macules and patches. Most common locations include the face, trunk, and extremities. Solitary CMs, larger CMs of up to 15 cm in diameter, and CMs with red, brown, or grey color may also be seen. Almost 50% of CMs will have a surrounding blanched halo, and occasionally arterial flow may be appreciated in some of these lesions. While these vascular stains are usually present at birth, they more generally tend to develop with time.

CM-AVM syndrome is an autosomal dominant condition and is most commonly caused by an inactivating mutation in the *RASA1* gene, which encodes p120-rasGTPase–activating protein. This protein appears to be integral to signaling for various growth factor receptors that control proliferation, migration, and survival of several cell types, importantly including vascular endothelial cells. While this condition has a very high penetrance (>95%), the clinical spectrum of number of CMs and presence of AVM/AVFs is broad. AVMs are observed in approximately 30% of patients and most commonly occur in the skin, muscle, and bone of the face, ears, thorax, and extremities, as well as in the brain and spine. The literature suggests that symptomatic intracranial and spinal AVMs occur in up to 7% of patients with CM-AVM and usually present in the first 7 years of life, with the possibility of significant morbidity.

Not all patients with CM-AVM will have the *RASA1* mutation. Orme et al performed a review of the published medical literature regarding *RASA1*-confirmed CM-AVM and found that a diagnosis of CM-AVM is probable in a patient presenting with more than three characteristic CMs. While for most affected individuals these vascular lesions are a benign finding, the presence of a subset of patients with potentially morbid intracranial and spinal AVMs makes diagnosing CM-AVM important. Using cutaneous findings to identify patients with asymptomatic latent intracranial and intraspinal AVM/AVF could be life-altering. We strongly advocate for imaging with MRI/MRA of the brain and spinal cord in children with suspected CM-AVM syndrome.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #8**

Presented by Lara Rosenbaum, MD, MHS and Monica Rani, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **Case #9**

Presented by Julia Minocha, MD, Jonathan Cotliar, MD, and Joaquin Brieva, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS
This 66 year-old Caucasian female with a history of orthotopic liver transplantation from a male donor for hepatitis C cirrhosis presented with a morbilliform and vesicular eruption on her face, trunk and extremities. The eruption was first noted 1 day prior and was not painful or pruritic. The patient also complained of fevers, abdominal pain and worsening fatigue. She denied diarrhea. She was admitted to the hospital for neutropenic fever 2 weeks prior. No source of infection was found, and she was discharged on a course of antibiotics.

PAST MEDICAL HISTORY:
Orthotopic liver transplantation from a male donor for hepatitis C cirrhosis 5 months prior, systemic lupus erythematosus in remission, stage 1 breast cancer s/p mastectomy, chronic obstructive pulmonary disease, atrial fibrillation

MEDICATIONS:
Granulocyte colony-stimulating factor, vancomycin, cefepime, ciprofloxacin, mycophenolate mofetil, prednisone, tacrolimus, atovaquone, valganciclovir, metoprolol, amlodipine, furosemide, aspirin

PHYSICAL EXAM:
On the trunk, extremities and face, there were diffuse purpuric macules and patches with a few scattered erosions and several intact vesicles and bullae.

LABS/IMAGING:
Abnormal: Hgb 7.6 g/dL (11.6-15.4 g/dL), WBC 2.6 K/UL (3.5-10.5 K/UL), Plt 58 K/UL (140-390 K/UL), AST 135 U/L (0-39 U/L), ALT 68 U/L (0-52 U/L), total bilirubin 1.1 mg/dL (0-1.0 mg/dL), direct bilirubin 0.6 mg/dL (0-0.2 mg/dL), alkaline phosphatase 233 U/L (34-104 U/L), LDH 2593 U/L (0-251 U/L), ferritin 45,751 ng/mL (11-307 ng/mL), triglycerides 289 mg/dL (50-150mg/dL), PT 17.1sec (9.2-13 sec), INR 1.6 (0.8-1.2), D dimer > 69,000 ng/mL (0-243 ng/mL), fibrinogen 113 ng/mL (221-498 ng/mL), EBV serum IgG positive, HSV 1&2 IgG equivocal, Hep B surface Ab positive, Hep B core Ab positive, ANA 1:40-1:80, C3 80 mg/dL (90-180 mg/dL).

Peripheral blood FISH analysis: XY (donor) 22%, XX 78%
Peripheral blood HLA typing: positive for circulating donor cells

Normal/Negative: Cr, EBV serum IgM, EBV serum PCR, HSV serum PCR, HIV, HHV-6 serum PCR, CMV quantitative, HIV Ab, HIV PCR, Hep B surface Ag, Hep B core IgM, C4, anti-DNA Ab, anti-Sm Ab, anti-RNP/Sm Ab, anti-SSA Ab, anti-SSB Ab, anti-dsDNA Ab, anti-Scl70 Ab.

HISTOPATHOLOGY:
Skin: There is an interface lymphocytic infiltrate with focal vacuolar changes of the basal cells and multiple necrotic epithelial cells at various levels of the epidermis. The epidermis shows focal hyperkeratosis. There is some dermal edema and telangiectasia with a perivascular and focally periadnexal lymphohistiocytic infiltrate. FISH analysis targeting the Y chromosome was performed and revealed rare cells containing the Y chromosome noted near the epidermis.
Bone marrow: partially necrotic hypocellular bone marrow with increased apoptotic/cellular debris, marrow damage and macrophages. T cells are predominantly CD8+. FISH analysis

revealed chimerism with XY (donor) 7.7%, XX 92.3%. Parvovirus B19, cytomegalovirus, Epstein Barr virus in-situ hybridization negative
Liver: liver with nodules of fungal organisms, GMS stain c/w candidal organisms, cannot rule out co-infection with *Cryptococcus*. No rejection.

DIAGNOSIS:
Solid organ graft-versus-host disease

TREATMENT AND COURSE:
The patient was hospitalized and had progressive disease with onset of diarrhea, worsening pancytopenia, neutropenia, cholestasis, renal failure and mental status changes leading to intubation. She also developed secondary hemophagocytic lymphohistiocytosis related to the GVHD. Aggressive treatment was initiated with pulse-dose methylprednisolone and cyclosporine without improvement. She received an allogeneic stem cell transplant from her daughter with anti-thymocyte globulin conditioning. She developed candidemia and polymicrobial bacteremia with *Enterococcus raffinosus* and an extended-spectrum beta-lactamase-producing *Klebsiella pneumonia*. Despite broad-spectrum antibiotic and antifungal therapy, she developed septic shock with progressive multi-organ failure and expired.

DISCUSSION:
Acute graft versus host disease (GVHD), although a common complication after hematopoietic stem cell transplantation (HSCT), is rare after solid organ transplantation. It is seen most commonly with liver (0.1-2%) and small bowel (5.6%) transplantation due to the high number of donor lymphocytes that are transplanted with the organ. It typically occurs 2-8 weeks post-transplant with skin rash, fever, pancytopenia and diarrhea. A morbilliform or vesicular eruption is the most common and often earliest clinical sign. Unlike GVHD seen in HSCT, the liver function is not affected because the transplanted liver lacks host antigen.

Risk factors for GVHD in the setting of liver transplantation still remain controversial. Recent studies have consistently identified shared HLA antigens between donor and recipient as a risk factor for the induction of GVHD. An HLA-match with a homozygous donor, results in one-way HLA matching in the donor's direction which favors GVHD. Conversely an HLA-match with a homozygous recipient results in one-way HLA matching in the recipient's direction which favors host-versus-graft rejection. Other possible risk factors include age of the recipient > 65 years, recipient-donor age difference ≥ 40 years, and immunodeficient states prior to transplantation such as diabetes mellitus, various autoimmune diseases, alcoholic liver disease and hepatocellular carcinoma.

The pathophysiology of solid organ GVHD is the result of an imbalance of power between the donor and recipient immune systems favoring the donor. Immunocompetent donor lymphocytes undergo activation and mount a destructive cellular immune response directed against the MHC of recipient tissues resulting in severe multisystem disease with a high mortality rate. Although donor lymphocytes can routinely be found in peripheral blood and bone marrow up to 100 days after OLT and are associated with a decreased risk of liver rejection, over time the immune system of the patient should reject the donor's lymphocytes and circulating cells should be of host origin only.

Diagnosis requires both clinical findings and the presence of macro-chimerism of T-cells which is defined as greater than 1% chimerism of T-cells in the peripheral blood. Allogeneic T-cells must be confirmed to be of donor origin to distinguish this entity from transfusion-related GVHD. FISH evaluation for sex chromosomes can help identify chimerism if the donor is the opposite gender; otherwise PCR or HLA typing can be used.

Treatment consists of infection prophylaxis including anti-bacterial, anti-viral and anti-fungal coverage as well as immune modulation. There is controversy regarding whether aggressive immunosuppression or restoration of the recipient's immune system by withdrawing immunosuppression is more effective. Immunosuppression with high-dose corticosteroids is the most commonly used treatment; however, this may increase the risk of infection and multi-organ failure. Anti-T cell antibodies have shown some success but are associated with an increased risk of post-transplantation lymphoproliferative disease and viral reactivation. Case reports have documented improvement with cytokine inhibitors including anti-TNF-a as well as allogeneic HSCT. Lastly, infusion of mesenchymal stem cells, which can differentiate into multiple cell lineages and have some immunosuppressive properties, have resulted in complete remission in 70-80% of treated children with a less robust response noted in adults.

The prognosis of solid organ GVHD is poor with a mortality rate of 80-100%. Slightly better outcomes have been reported in the pediatric population. The most common cause of death is sepsis with multi-organ failure highlighting the importance choosing a treatment regimen that includes infection prophylaxis and minimizes organ toxicity. Early recognition and diagnosis of this entity is critical for survival.

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Fast Break C

Presented by Lisa Shen, MD, Gil Abramovici, MD, Adnan Mir, MD, Monica Rani, MD, Joaquin Brieva, MD, and Amy Paller, MD
Department of Dermatology, Feinberg School of Medicine, Northwestern University

HISTORY OF PRESENT ILLNESS

A 15 year-old female with history of Darier disease presented to the hospital after returning from a school trip to Peru with a "sore" on the scalp and a one-day history of severe headache in the same region.

What is your leading diagnosis?

What is the most important test in the additional work up of this patient?

CHICAGO DERMATOLOGICAL SOCIETY **Case #10**

Presented by Nilanthi Gunawardane, MD and Jonathan Cotliar, MD
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HISTORY OF PRESENT ILLNESS
This 43 year-old African American male with hepatosplenic gamma-delta T-cell lymphoma presented with a new rash on day 15 following a double cord blood hematopoietic stem cell transplant. The rash involved his face, chest, arms, abdomen and back. The affected areas were itchy but not painful. The patient had persistent febrile neutropenia with no clear source of infection. He was started on broad-spectrum antibiotics and anti-fungals. The patient reported mild shortness of breath and diarrhea over the preceding few days.

PAST MEDICAL HISTORY:
Hepatosplenic gamma-delta T-cell lymphoma - first diagnosed in 12/2012; underwent one cycle of CHOP chemotherapy followed by 4 cycles of high-dose methotrexate and cytarabine; umbilical cord blood hematopoietic stem cell transplant

MEDICATIONS:
Vancomycin, cefepime, voriconazole, micafungin, cyclosporine, mycophenolate mofetil, ondansetron, valacyclovir, pentamidine, salt and soda mouthwash

PHYSICAL EXAM:
Skin examination was notable for erythematous macules and thin papules coalescing on the chest and abdomen; diffuse erythema of the face, neck and back; and mild oral mucositis.

LABS/IMAGING:
Abnormal:
WBC 0.4 (3.5-10.5 K/UL), ANC 0.0 (1.5-8 K/UL), Hgb 9.5 (13-17.5 g/dL), Plt 9 (140-390 K/UL), total bilirubin 2.2 (0-1.0 mg/dL)
Chest X-ray: Mild pulmonary edema and trace bilateral pleural effusions

Normal/Negative:
Chem 7, ALT, AST, Alk phos, urinalysis, bacterial and fungal blood cultures, urine cultures, Histoplasma urine antigen, Blastomyces urine antigen, 1-3 β-D glucan, cryptococcal antigen, Aspergillus galactomannan, Legionella urine antigen, strep urine antigen, Pneumocystis DFA, CMV viral load, stool Cyclospora, Giardia, Cryptosporidium, Microsporidium, ova and parasites and *C. difficile* PCR

HISTOPATHOLOGY:
Mild interface dermatitis with necrotic keratinocytes

DIAGNOSIS:
Pre-engraftment syndrome

TREATMENT AND COURSE:
The patient was started on intravenous steroids with improvement in his skin eruption, respiratory symptoms and diarrhea.

DISCUSSION
Hematopoietic stem cell transplantation is an important treatment modality for patients with hematologic malignancies and severe immune-mediated diseases. For patients who are unable

to find matched sibling or unrelated donors, umbilical cord blood (UCB) transplants are becoming an increasingly viable alternative. The number of UCB transplants performed in the US has continued to rise over the past several years. Patients who receive UCB transplants are thought to have a lower risk of chronic GVHD and an increased risk of graft-versus-malignancy effect compared to non-UCB stem cell transplant recipients. However, the time to engraftment is longer in UCB transplants and hence these patients are at risk for infection for a longer time when compared to non-UCB transplant recipients.

Pre-engraftment syndrome (PES) is a newly described entity that is thought to occur in patients who have undergone an UCB transplant. Although no definitive criteria for diagnosis have been established, characteristics of this syndrome include non-infectious fever (>38.3 C) unresponsive to antimicrobials, rash, pulmonary infiltrates, diarrhea, jaundice and weight gain. As the name implies, PES occurs prior to neutrophil engraftment, which is defined as an ANC of greater than 500 for 3 consecutive days. PES is a clinical entity, and there are no biochemical markers or specific histopathological findings that confirm the diagnosis. PES and acute GVHD share several clinical features, but the former develops prior to engraftment.

The incidence of PES is estimated to be between 20-70% of all patients who undergo UCB transplantation. The median time to development of PES is approximately 7-9 days following transplant. PES is thought to occur due to a cytokine storm arising from the donor cord blood cells. Prophylaxis with steroids decreased the incidence of PES by five-fold in one study.

Recognizing the symptom complex of PES is important because treatment with a short course of systemic corticosteroids will result in the resolution of symptoms. PES is not thought to be associated with significant morbidity or transplant-related mortality, although limited data exist. It has been shown that patients who develop PES have a higher rate of engraftment. In one study, the rates of engraftment among patients who developed PES and those who did not develop PES were 92% and 77% respectively.

It is important to distinguish PES from engraftment syndrome. Engraftment syndrome, characterized by fever without infectious source, rash, non-cardiogenic pulmonary edema, renal dysfunction and/or hepatic dysfunction is a manifestation of increased capillary permeability. Engraftment syndrome occurs around the time of engraftment, most commonly within 96 hours of engraftment as defined above. It can occur following autologous or allogeneic hematopoietic stem cell transplantation. Engraftment syndrome, as opposed to PES, is associated with increased transplant-related mortality, specifically due to pulmonary complications and multi-organ failure. Treatment consists of high-dose steroids and supportive care.

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CHICAGO DERMATOLOGICAL SOCIETY **Case # 11**

Presented by Lauren Graham, MD, PhD and Joan Guitart, MD
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HISTORY OF PRESENT ILLNESS
This 55 year-old Caucasian male presented in 2007 with a 1.5 year history of an erythematous, indurated plaque on his face and neck. Biopsy revealed nodular amyloidosis. Blood work revealed increased IgM and increased free κ light chain. Bone marrow biopsy was consistent with Waldenstrom's macroglobulinemia. Abdominal fat pad aspiration revealed deposition of amyloid. Work up for involvement of other organs systems was negative for amyloid deposition. Patient was treated with bortezomib, rituximab, and dexamethasone. Eight weeks after treatment, his Waldenstrom's macroglobulinemia was considered in remission and his cutaneous amyloidosis improved. Patient presented in September 2013 with a 6-month history of new lesions and increased induration of his pre-existing amyloidosis lesions.

PAST MEDICAL HISTORY: Waldenstrom's macroglobulinemia (lymphoplasmacytic lymphoma)

MEDICATIONS: none

FAMILY HISTORY: Mother with Waldenstrom's macroglobulinemia, father with basal cell carcinoma

REVIEW OF SYSTEMS: neuropathy in his hands. All other review of systems was negative.

PHYSICAL EXAM: On the bilateral cheeks and inferior forehead, there were confluent indurated and erythematous plaques with overlying telangiectasia. The neck had multiple thin yellow-orange linear to oval plaques. No lymphadenopathy was noted.

LABS/IMAGING:
Abnormal:
Quantitative IgG 603 mg/dL (700-1600 mg/dL), Quantitative IgA 58 mg/dL (70-400 mg/dL), Free κ Light Chain 4.14 mg/dL (0.33-1.94 mg/dL,), Free λ Light Chain 0.25 mg/dL (0.57-2.63 mg/dL), K/L Light Chain Ratio: 16.56 (0.26-1.65), 24-hour urine protein: <120 MG/TV (50-80 MG/TV), Platelets 112 K/uL (140-390 K/uL)

Normal/Negative:
24-hour UPEP, SPEP, LFTs, Chem7, Ca, Mg, Phos, LDH, Quantitative IgM

HISTOPATHOLOGY:
Skin: The epidermis is unremarkable. Within the dermis, there were extensive deposits of amorphous amphophilic material extending into the deep reticular dermis with prominent perivascular distribution. Changes were consistent with those of light chain-related amyloidosis.
Bone marrow: no phenotypically abnormal B cells

DIAGNOSIS:
Nodular amyloidosis in the setting of previous Waldenstrom's macroglobulinemia

TREATMENT AND COURSE:
The patient was treated with bortezomib, rituximab, and dexamethasone in early 2008. Repeat bone marrow biopsy after 8 weeks of treatment revealed no evidence of disease. His skin lesions improved, and his Waldenstrom's macroglobulinemia was considered in remission. In 2013, he

began developing new skin lesions and worsening of old lesions that were consistent with amyloidosis. Since development of skin lesions was his initial presentation of his Waldenstrom's macroglobulinemia, further work up was performed. Bone marrow biopsy did not show evidence of reoccurrence. Imaging does not show evidence of involvement of other organ systems. Patient currently is determining whether he wants to pursue prophylactic treatment for systemic amyloidosis.

DISCUSSION:

Amyloidosis refers to a group of diseases that are characterized by abnormal deposition of proteinaceous material into the skin and/or other organs. There are 28 known sources of amyloid that can deposit in organs, including keratin, amyloid associated protein (AA), apolipoprotein A, β2-microglobulin, Aβ precursor protein, immunoglobulin light chains, and immunoglobulin heavy chains. Amyloid deposits in the skin can manifest as waxy, indurated, erythematous, yellow, violaceous, translucent, and/or sclerodermoid papules, plaques, and nodules. Nodular amyloidosis results from the deposition of immunoglobulin light chains (AL). The lambda isotype is four times as common as the kappa.

Histopathology of nodular amyloidosis reveals amorphous, eosinophilic deposits in the dermis which can extend to the subcutis and blood vessel walls. Amyloid stains positive for Congo red with green birefringence. Immunostaining is positive for lambda or kappa light chains. Nodular amyloidosis can be associated with plasma cell dyscrasias, multiple myeloma, Sjögren syndrome, and subacute cutaneous lupus erythematous. When a skin biopsy reveals nodular amyloidosis, investigation of an underlying plasma cell dyscrasia is warranted. In addition to the skin, systemic amyloidosis can affect many organs resulting in bone marrow involvement, a restrictive cardiomyopathy, congestive heart failure, neuropathy, proteinuria and edema, or hepatomegaly. Patients may experience lethargy, fatigue, weight loss, edema, diarrhea or constipation, postural hypotension, and/or purpura. Work up for systemic amyloidosis may include serum protein electrophoresis, urine protein electrophoresis, LDH, quantitative light chains, uric acid, 24-hour urine protein, troponin-T, amino-terminal pro-natriuretic peptide type-B (NT-proBNP), skin biopsies, bone marrow biopsies, echocardiogram, abdominal subcutaneous fat pad aspiration, labial salivary gland biopsy, and/or rectal mucosal biopsies performed with colonoscopy.

Treatment options for systemic amyloidosis due to light chain immunoglobulins include high-dose melphalan followed by autologous stem cell transplantation, various chemotherapy regimens, or clinical trials. Chemotherapy regimens include bortezomib, melphalan, dexathemasone (BMDex); cyclophosphamide, thalidomide, dexamethasone (CTD); or cyclophosphamide, bortezomib, dexamethsone (CyBorD). Treatment is imperative to prevent or reduce end-organ damage, the main cause for the25-30% early death rate seen in primary systemic amyloidosis. Amyloidosis caused by light chain immunoglobulins can be a rapidly progressive disease, highlighting the importance of early detection. Patients may present earlier with skin manifestations than the sequela of other effected organs, giving dermatologists an important role in early diagnosis.

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