Chicago Dermatological Society

May 2014
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, May 21, 2014
Rush University Medical Center

Conference Host:
Department of Dermatology
Rush University Medical Center
Chicago, Illinois

Program

Committees & Registration

8:00 a.m. - 9:00 a.m.	CDS Plans & Policies Committee
9:00 a.m. - 10:00 a.m.	IDS Board Meeting

Program Activities

8:30 a.m.	Registration, Continental Breakfast & Exhibitor Time Searle Conference Center
9:00 a.m. - 10:00 a.m.	RESIDENT LECTURE "IgE Autoimmunity" Janet A. Fairley, MD *Room 542 Brainard*
9:30 a.m. - 10:45 a.m.	Clinical Rounds – Patient Viewing *Room 264 Professional Building (Elevator III)* Slide Viewing *Room 538 (Fenger)*
11:00 a.m. - 12:00 p.m.	General Session *Room 542 (Brainard)*
11:00 a.m.	FREDERICK MALKINSON LECTURE "Bugs, Brains and Blisters: An Update on Bullous Pemphigoid" Janet A. Fairley, MD
12:00 p.m. - 12:40 p.m.	Box Lunches & Visit with Exhibitors *Main Dining Area - Room 500*
12:40 p.m. - 12:50 p.m.	CDS Business Meeting *Room 542 (Brainard)*
12:50 p.m. - 2:30 p.m.	Case Discussions and MOC Questions *Room 542 (Brainard)*
2:30 p.m.	Meeting adjourns

Mark the Date!

Next CDS monthly meeting – Wednesday, June 11, 2014
Loyola University Medical Center; Maywood
Watch for details on the CDS website: www.ChicagoDerm.org

Guest Speaker

Frederick Malkinson Lecture

Janet A. Fairley, MD

Chair and John S. Strauss Professor of Dermatology
University of Iowa Carver College of Medicine
Iowa City, IA

Education

BS, Zoology, Michigan State University
MD, University of Michigan Medical School
Dermatology Residency, University of Michigan
Fellowship, NIH Research in Cell Physiology, University of Michigan

Research Interests and Publications

The overall goal of the Fairley laboratory is to better understand the pathogenesis of the autoimmune blistering diseases of the skin. Bullos pemphigoid is a blistering disease characterized by autoantibodies directed against BP 180, a cell-substrate attachment protein of the hemisdesmosome.

Dr. Fairley is the author or co-author of numerous journal articles and other publications.

Chicago Dermatological Society

"Chicago Dermatological Society Monthly Meeting Series"

May 21, 2014 Chicago, IL

OBTAINING YOUR CERTIFICATE OF CREDIT

Participants must attend the entire session to receive credit. Please be sure to sign the attendance list at 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

Janet A. Fairley, MD; Chair and John S. Strauss Professor of Dermatology, University of Iowa Carver College of Medicine; Iowa City, IA

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.

Janet A. Fairley, MD, has no significant financial relationships to disclose.

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

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NOTES

NOTES

Presented by Jessica Hsu, MD, and Mark Hoffman, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 20-year-old Caucasian man presented to clinic with a 5-month history of firm swellings initially starting on the left lateral lower eyelid, with additional lesions developing on the left lateral upper eyelid and right medial upper lip in the following 1-2 weeks. The lip lesion was extremely sensitive to hot and cold foods, while the eyelid lesions made it difficult for the patient to wink and fully close his eye. He developed blurred vision 3 weeks after development of the eyelid lesions.

At the time of presentation, the patient had already failed a 5-day course of prednisone 40 mg daily, and had taken fexofenadine 180 mg every morning with cetirizine 10 mg nightly without any improvement. He had been placed on a cinnamon and benzoate-free diet by a nutritionist without prior allergy testing to these agents, and did not experience any improvement in his condition. CTs of the chest and head, and a colonoscopy had been performed and were unremarkable.

The patient denied any fevers, chills, night sweats, unintentional weight loss, headaches, periodontal symptoms, shortness of breath, cough, sputum, hemoptysis, chest pain, nausea, vomiting, diarrhea, constipation, bloody stools, or abdominal pain.

PAST MEDICAL HISTORY

None

MEDICATIONS

Multivitamin

FAMILY HISTORY

Mother - seronegative rheumatoid arthritis

SOCIAL HISTORY

No illicit drug use or tobacco
Occasional alcohol consumption, on the weekends and in social settings

PHYSICAL EXAM

On the left lateral upper and lower eyelid, there were ill-defined subcutaneous firm pink swellings. The pupils were equal, with no ocular movement abnormalities on exam. He was unable to completely close the left eye. On the right medial upper cutaneous lip, there was an approximately 2.5cm ill-defined indurated rubbery nodule extending slightly past the midline onto the left upper lip. The patient's tongue was normal, without any visible deviation. There was no palpable cervical, submental, preauricular, or supraclavicular lymphadenopathy.

HISTOPATHOLOGY

An incisional biopsy of the right medial upper lip performed at an outside institution was reviewed and found to demonstrate squamous mucosal epithelium with a moderately dense predominantly histiocytic infiltrate with an admixture of lymphocytes and plasma cells located in the deeper portions of the biopsy specimen. There was no necrosis or polarizable foreign body

material. PAS, GMS, Fite and AFB stains were negative. A CD68 immunostain highlighted the histiocytic proliferations. CD1a and S-100 immunostains were non-contributory.

LABORATORY RESULTS

Initial Lyme screen ordered by infectious disease was positive, however repeat testing was negative.

The following tests were negative or normal:
CMP, CBC with diff, TTG IgA, Endomysial IgA, IBD Serology Panel, ESR, RPR, ANA, RF, Hep B surface antigen, Hep B core antibody, PPD, Quantiferon gold

RADIOLOGY AND DIAGNOSTIC TESTING

EGD and colonoscopy showed gastritis, with no evidence of inflammatory bowel disease. CT scan of the head and MRI of the brain were negative. CT scan of the chest was negative. Pulmonary function testing demonstrated mild obstructive physiology reversible after inhaled bronchodilators, suggestive of improved effort, and was otherwise normal. The patient was evaluated by ophthalmology and noted to have a left CN7 palsy.

DIAGNOSIS

Melkersson-Rosenthal Syndrome

TREATMENT AND COURSE

The patient was initially placed on prednisone 60 mg PO QAM with calcium and vitamin D supplementation, minocycline 100 mg PO BID, and pentoxifylline 400 mg PO TID. He did not follow up until 4 months later, at which point he admitted to non-compliance with therapy. He was still taking the prednisone 60 mg PO QAM, and was only taking minocycline once daily and pentoxifylline twice daily. He did note significant improvement, with resolution of the eyelid lesions and reduction in size of lip lesion; the eye weakness however persisted. The patient was counseled on the importance of therapeutic and follow-up compliance, and advised to start hydroxychloroquine 200 mg PO BID while the prednisone was tapered and discontinued. He has been off the prednisone now for about 2 months, and has remained on the regimen of hydroxychloroquine 200 mg PO BID, minocycline 100 mg PO BID, and pentoxifylline 400 mg PO TID for the past 5 months, although his compliance taking these medications has at times continued to be poor.

The patient most recently reported some additional improvement with the medial upper lip lesion decreasing in size. However, he noted a new area of swelling of the right upper eyelid and new blurred vision and tearing of the right eye. He continues to have difficulty closing the left eye completely, though the blurred vision in the left eye has now completely resolved. He continues to be followed routinely by ophthalmology and dermatology. Methotrexate is being considered as an adjuvant therapy in the future pending his response to the current regimen.

DISCUSSION

Melkersson-Rosenthal syndrome (MRS) is a triad of recurrent orofacial edema, relapsing facial palsy, and fissured tongue. The classic triad is rarely seen, with complete forms of MRS constituting only 8-25% of cases. Symptoms may occur at different intervals of months to years, thus monosymptomatic and oligosymptomatic forms of MRS are much more frequently seen. The most typical feature is swelling of the orofacial region. Localized, episodic, noninflammatory swelling of the lip is known as cheilitis granulomatosa. MRS is a rare disease with equal gender and race distribution. Symptoms usually present in young adults, though children may be affected, particularly with cheilitis granulomatosa.

Clinically, the orofacial edema is the most important and consistent symptom of MRS, and is often the presenting complaint. Swelling is typically asymmetric and unilateral, described as painless, nonpruritic, firm edema. The swelling can occur at irregular intervals, with incomplete resolution between episodes, resulting in granulomatous inflammation that is firm and indurated. The facial palsy characteristically has a sudden onset, is indistinguishable from Bell's palsy, tends to be unilateral, and clears spontaneously. It may recur in up to 10% of patients. The lingua plicata or fissured tongue of MRS appears to be the least important and least common feature of the classic triad. The plicated tongue typically demonstrates deep grooves on the dorsal surface, and the tongue itself may be enlarged or exhibit diminished taste sensation or paresthesias.

Several disorders have been associated with MRS, including ophthalmologic findings such as lagophthalmos, exposure keratitis, retrobulbar neuritis, and paralysis of eye muscles. Neurologic manifestations such as hyperhidrosis, dysgeusia, paresthesias, hyperacusis, and migraine or cluster headaches have been described.

On histology, the characteristic finding in MRS is noncaseating granulomas. However, their absence does not exclude MRS, since dilated lymphatics with perivascular infiltrates of histiocytes, lymphocytes, and plasma cells in the mileu of nonspecific edema can be the hallmark of early lesions. The lip is the most commonly biopsied site. MRS can be difficult to diagnosis since the classical features may not always be present at the same time and because the noncaseating granulomas may not always be seen. The diagnosis hinges on clinicopathologic correlation, and other entities such as oral Crohn's disease, sarcoidosis, tuberculosis, tuberculoid leprosy, pyostomatitis vegetans, contact hypersensitivity reactions, angioedema, and lupus vulgaris should be considered in the differential.

Treatment of MRS is a challenge, and there are no uniformly predictable successful therapies described in the literature. This is partly because the etiology of this condition remains obscure. No consistent factor has been elucidated, and hypotheses regarding hereditary factors, infectious agents, allergies, and vasomotor disturbances remain invalidated. Although extremely rare, any underlying associations such as sarcoidosis, Crohn's disease, or odontogenic infections should be ruled out. MRS has also been imputed to allergic hypersensitivity, particularly to cinnamic aldehyde and alcohol, in addition to metals such as cobalt. The mainstay of therapy is corticosteroids, both systemic and intralesional. Other anti-inflammatory agents such as clofazimine, hydroxychloroquine, dapsone, sulfapyridine, danazol, and broad-spectrum antibiotics such as tetracycline, metronidazole, and sulfa drugs have been utilized with variable success. More recent reports with infliximab, thalidomide, and methotrexate have been described. Surgical approaches, such as reduction cheiloplasty, should be reserved only for severe and cosmetically disfiguring cases.

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Presented by Sherri Korman, MD and Warren Piette, MD
Department of Dermatology, RUSH University Medical Center

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 3**

Presented by Emily Garritson, MD and Michael Tharp, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 56-year-old Chinese male with a past medical history of hypertension presented to clinic with an 8-year history of pruritic papules that initially erupted on his lower legs. Over the past few years, the lesions spread to involve his upper extremities, trunk, and eventually his face. The patient described severe pruritus associated with the lesions. He denied any specific new medications prior to the onset of the lesions, but he did note taking numerous Chinese herbal preparations for health maintenance. When the lesions increased in distribution, he sought evaluation at an outside institution where he underwent two skin biopsies. One biopsy taken from the right chest demonstrated a perivascular dermatitis with many eosinophils consistent with a hypersensitivity reaction, and the other biopsy obtained from the left knee was read as consistent with lichen simplex chronicus. The patient was treated with oral antihistamines and clobetasol ointment with no improvement in his pruritus or the lesions. He also tried a trial of triamcinolone ointment without success.

PAST MEDICAL HISTORY

Hypertension

MEDICATIONS

Lisinopril
Hydrochlorothiazide
Chinese herbal supplements

ALLERGIES

There were no known drug allergies.

FAMILY HISTORY

The patient's family history was significant for hypertension in his maternal grandmother. He also had a brother with childhood eczema.

SOCIAL HISTORY

The patient denied any illicit drug use. He reported occasional alcohol consumption (approximately one beer per week). He is a former cigarette smoker and quit smoking in 1998.

PHYSICAL EXAM

At the time of the initial examination, the patient had numerous erythematous papules and plaques scattered on his face, trunk, and extremities. The lesions had an urticarial-like appearance. Several of the lesions had eroded. There were no intact vesicles or bullae. There were no lesions observed on the oral mucosa or conjunctivae.

HISTOPATHOLOGY

Two punch biopsies from the right axillae and right plantar foot demonstrated a "spongiotic dermatitis" with a superficial perivascular eosinophilic lymphocytic infiltrate. Direct immunofluorescence findings of perilesional skin were positive for IgG deposited at the basement membrane zone, consistent with bullous pemphigoid.

LABORATORY RESULTS

The patient's CBC was unremarkable, and his CMP was normal with the exception of an elevated blood glucose level of 170. The patient was taking oral prednisone at the time of the blood draw. An aerobic culture obtained from an eroded lesion yielded light growth of methicillin sensitive *Staphylococcus aureus*.

DIAGNOSIS

Urticarial bullous pemphigoid

TREATMENT AND COURSE

The patient's lesions were biopsied and cultured at the initial visit. He was given a 10-day course of cephalexin 500 mg to be taken four times a day. Once the results of the biopsy were evident, he was started on prednisone 40 mg daily. The patient reported his symptoms had improved by 50% in the first 2 days and 90% in the first week of starting the prednisone. He was also applying hydrocortisone 2.5% ointment to the lesions on his face twice a day and clobetasol ointment to the lesions on his body twice a day. After two weeks of prednisone, the patient was also started on dapsone 25 mg daily. Prednisone was tapered to zero over the course of approximately three months, while the dapsone was increased to 100 mg daily. The patient has been clear of lesions for two months, and he remains on dapsone 75 mg daily. Of note, the patient suffered two retinal detachments of the right eye since the time of diagnosis.

DISCUSSION

Bullous pemphigoid is an acquired autoimmune blistering disorder characterized by autoantibodies to two hemidesmosomal antigens designated as BP180 and BP230. BP180 is a transmembrane protein that spans the lamina lucida, and BP230 is an intracellular protein of the plakin family found in basal keratinocytes. Bullous pemphigoid is the most common subepidermal bullous disease. The disorder typically affects adults over 70 years of age; however, it can rarely present in younger adults, and there have been cases reported in infants and children. Men appear to be affected more often than women.

The classic bullous lesions of bullous pemphigoid are the result of subepidermal blister formation at the dermal-epidermal junction through an antibody mediated process. The primary factor in the pathogenesis of this disease is IgG directed against the NC16A region of BP180. Further studies have also shown the importance of IgE autoantibodies to BP180 in the development of the disorder. Both antibody isotypes lead to the increased production of IL-6 and IL-8, which are critical to the disease process. Approximately 90% of patients will have specific IgG and IgE autoantibodies for BP180. It has also been shown that 70% of untreated patients will have an elevated level of peripheral blood IgE. IgE autoantigen mast cell degranulation underlies the initiation of the inflammatory cascade that results in the formation of the urticarial appearing lesions of bullous pemphigoid.

The clinical presentation of bullous pemphigoid can be quite variable. The classic appearance is described as tense vesicles or bullae with clear fluid on normal-appearing or erythematous skin. These bullous lesions are usually seen in combination with urticarial papules. The lesions have an overall symmetric distribution and generally arise on the abdomen and flexural extremities. Between 10-20% of patients will have oral lesions, but other mucosal sites are rarely involved. Individual bullous lesions are present for several days and subsequently resolve with erosions and crusting. Nearly all patients report severe pruritus associated with the lesions. The onset of the blisters can be preceded by a prodrome of intractable pruritus with possible associated urticarial papules and plaques lasting for weeks to months.

The literature has shown that approximately 20% of patients with bullous pemphigoid will lack the classic bullous phenotype. One recent case series of 15 patients with non-bullous skin lesions but characteristic immunopathologic findings for bullous pemphigoid described the heterogeneous array of presentations, which included eczematous plaques, erythematous papules and nodules, urticarial plaques, and pruritus sine material. Other reports have documented cases of patients with lesions suggestive of prurigo nodularis and erythema-multiforme. Patients without the classic bullous lesions are often misdiagnosed initially with other pruritic disorders, so it can take several years to arrive at the correct diagnosis. Therefore, it is prudent to consider bullous pemphigoid in the differential diagnosis for older patients with pruritus even if the patient does not have classic bullous lesions.

The diagnosis of bullous pemphigoid is based upon characteristic clinical features, histologic features on biopsy, serology, and direct and indirect immunofluorescence microscopy studies. The biopsy of non-bullous lesions may demonstrate subepidermal clefting, dermal infiltration of eosinophils, and eosinophilic spongiosis. Microscopic examination of early bullous lesions will reveal a subepidermal blister with a dermal infiltrate of eosinophils and mononuclear cells. Electron microscopy studies show that the blister is formed in the lamina lucida. Direct immunofluorescence of perilesional skin will result in a linear deposition of IgG and/or C3 at the basement membrane zone. Immunoprecipitation studies have shown that 60-100% of patients' sera have IgG autoantibodies against BP180 and BP230.

Bullous pemphigoid is a chronic disease with exacerbations and remissions. The majority of patients undergoing treatment will achieve remission, but there is a significant risk of mortality in older patients. The literature has shown the 1-year mortality rate to be between 10% and 40%. ELISA studies have demonstrated that the serum level of IgG and IgE autoantibodies to BP180 are correlated with disease severity. It has also recently been shown that high levels of anti-BP180 autoantibodies and a positive direct immunofluoresence are reliable indicators for future relapses.

Systemic corticosteroids are considered the mainstay of treatment for bullous pemphigoid. Patients with widespread, diffuse lesions are started on a course of oral prednisone dosed between 0.5-1 mg/kg/day. The lesions generally respond in 1-2 weeks, and the dose of prednisone is tapered over the course of several months. The literature has also supported the use of potent topical corticosteroids, which have been reported to have similar efficacy to systemic corticosteroids with significantly less side effects. Immunosuppressant drugs including azathioprine, methotrexate, mycophenolate mofetil, chlorambucil, and cyclophosphamide have also been utilized. Smaller studies have shown the success of dapsone and the combination of nicotinamide and minocycline in milder cases. Severe, treatment-resistant cases can be treated with IVIg, plasma exchange, or rituximab.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 4**

Presented by Blake Troiani, MD, and Arthur Rhodes, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 7-year-old light skin colored Hispanic male presented for evaluation of a lesion on the right mid back. Per the patient's mother, the lesion had been present approximately 2 months, having started as a small brown spot that subsequently grew vertically. The lesion was stated to be tender and occasionally bleeding when manipulated. Antibiotic ointment had been applied to the lesion on occasion. Otherwise, there was no treatment. The patient had no history of mole removal. A review of systems was normal. There was no family history of melanoma.

PAST MEDICAL HISTORY

No contributory history

MEDICATIONS

None

ALLERGIES

None

FAMILY HISTORY

No family history of skin cancer or other malignancies.

SOCIAL HISTORY

The patient lives with his family. No one in the household is a smoker. He plays soccer, and performs well in school.

PHYSICAL EXAM

On the upper back on the right side, a 1 cm polypoid mass with focal areas of crusting was noted. The lesion was approximately 1 cm in height. There was no sun-induced freckling. Hair color was dark brown. The eye color was uniform brown. His nevus pattern was benign otherwise.

HISTOPATHOLOGY

Histopathology demonstrates a polypoid exophytic mass transected at the base. The epidermis demonstrates prominent ulceration with areas of epidermal effacement. The epidermis also contains nests of cells with pigmentation distinct from other nests in the lesion. The inferior margin is involved. In the dermis, coalescing sheets and fascicles of spindled and epithelial cells that show no evidence of maturation are seen, although smaller nests are noted at the base of the lesion. These cells stained with S100 and melan-A. Ki-67 showed positive staining in approximately 25% of the atypical, present throughout the lesion, including the deep margin. An increase in dermal vascularity is seen. Mitoses are easily found within the dermal component, 6 per mm^2, with atypical mitoses noted. FISH analysis was completed, revealing deletions of 6q23 in > 50% of enumerated cells.

LABORATORY RESULTS

None

RADIOLOGY
Total body PET (9/12/2013) showed no fluorine-18-fluorodeoxyglucose avid lesions.

DIAGNOSIS
Spitzoid melanoma

TREATMENT AND COURSE
The patient was referred to a pediatric surgeon for re-excision of the lesion under general anesthesia. One month after the initial biopsy, a re-excision with 1 cm margins was performed. A sentinel lymph node biopsy was not performed. The re-excision demonstrated a 2 mm deep proliferation of fascicles of epithelioid and spindled cells similar to the original biopsy. Margins were clear. A total body PET scan performed one month after re-excision did not reveal suspicious lesions. Eight months after his initial presentation, he presented for follow up in dermatology with no new or changing lesions. His review of systems was normal. He will be followed in the dermatology clinic for full mucocutaneous surveillance every 3 months for the next 2 years and every 6 months thereafter.

DISCUSSION
Spitz tumors represent a distinct group of melanocytic tumor most often seen in children. Although the majority of these lesions are considered benign, a subset of Spitz nevi demonstrates features histopathologically consistent with melanoma. This subset of Spitz nevi poses substantial diagnostic difficulty, even among experts, due to its resemblance to melanoma. Such lesions have been termed atypical Spitz tumors.

Distinguishing among atypical Spitz tumors, Spitzoid melanomas, and conventional melanomas presents a unique challenge to the dermatopathologist and to the clinician; however, the distinction is an important one upon which prognosis and clinical management depend. Despite their clinical appearance, atypical Spitz tumors may show greater than expected cytologic atypia, with large, pleomorphic cells with prominent nucleoli and high nuclear-to-cytoplasmic ratios, large tumor size (>1 cm), ulceration, lack of maturation and a pushing border. Deep mitoses, focal necrosis, and pagetoid spread are also features of melanoma that can be seen in these lesions. Of note, atypical mitoses may be occasionally seen in Spitz nevi and are not limited to atypical Spitz tumors.

Given the overlap of histologic features seen among Spitz nevi, atypical Spitz tumors, Spitzoid melanomas, and conventional melanomas, several pathohistologic, immunohistochemical and molecular features have been analyzed to improve diagnostic accuracy. Pathohistologic features that have been associated with more aggressive behavior include ulceration, asymmetry, high-grade cellular atypia, high mitotic rate (>6 per mm^2) and the presence of deep mitoses. HMB-45, a melanogenesis-related protein, has been used to demonstrate a lesion's maturation. Diffuse scattered HMB-45 positivity has been associated with melanoma, while top-heavy staining is suggestive of a benign lesion. Recent investigations suggest, however, that maturation should not be heavily weighed when evaluating atypical Spitz tumors with regard to clinical behavior. Ki-67 is a protein expressed by cells that have progressed to the late G1 phase of the cell cycle, making it a useful marker of cellular proliferation. Spitz nevi tend to demonstrate Ki-67 positivity in the upper regions of the lesion. In contrast, melanoma shows Ki-67 staining scattered throughout the lesion, including the deep margin. Overlap in proliferation indices for atypical Spitz tumors and melanoma limits the utility of Ki-67 a single reliable marker for distinguishing the two entities. CD99, a transmembrane glycoprotein involved in apoptosis and adhesion, has shown different levels of expression in melanomas versus Spitz nevi. Fifty-six percent of Spitzoid melanomas and 60% of conventional melanomas versus only 5% of

Spitz nevi demonstrated CD99 expression. Identifying B-raf and N-ras mutations to distinguish these entities has not been useful.

More recently, studies focused on the utility of identifying specific chromosomal abnormalities identified by fluorescent in-situ hybridization (FISH) have provided new insight into the diagnosis of atypical Spitz tumors and predicting their behavior. Gerami and others have shown that atypical Spitz tumors with homozygous 9p21 deletions, 6p25 gains and/or 11q13 gains demonstrated a significant association with tumor progression beyond the sentinel lymph node. Tumors with isolated deletions in 6q23, on the other hand, did not behave differently from tumors lacking abnormal findings on FISH. Compared with all atypical Spitz tumors demonstrating copy number aberrations on FISH, those with homozygous 9p21 deletions maintained a significant association with progression beyond the sentinel lymph node, including distant metastasis and death. Although there remains insufficient data to classify these lesions based solely on FISH analysis, it remains a fertile field for continued investigation.

Management of atypical Spitz tumors remains challenging and controversial. In the past, sentinel lymph node (SLN) biopsies were routinely performed in the case of atypical Spitz tumors in an attempt to predict metastatic potential. Studies investigating the utility of SLN biopsy in the case of atypical Spitz tumors have shown SLN positivity in 17% to 71% compared with the reported rate of 16% in conventional melanomas. Although atypical Spitz tumors frequently involve SLNs, involvement beyond the SLN is rare (<3%), and death from atypical Spitz tumors is reported in less than 0.5% of cases. These data suggest that SLN biopsy is of little value in predicting the prognosis of these lesions. Patients with a positive node related to an atypical Spitz tumor tend to have an overall better prognosis than patients with positive nodes related to conventional melanoma. SNL may, therefore, be best reserved for consideration on a case-by-case basis. With regard to surgical management of patients with atypical Spitz tumors, there is currently no consensus regarding excision margin, although some authors suggest excising atypical tumors with margins up to 1 cm. Metastasis and death have been documented in at least one patient with an incompletely excised atypical Spitz tumor.

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Fast Break #1

Presented by Emily Garritson, MD and Brian Bonish, MD, PhD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

The patient is a 39-year-old white female who presented to clinic with reports of asymptomatic hyperpigmentation of the mid-chest and inframammary folds for 5 years. The hyperpigmentation had been progressively increasing in distribution over time and now involved her bilateral axillae and upper abdomen. The patient also noted a twenty-year history of hidradenitis suppurativa with cyst-like lesions in the bilateral axillae, chest, and groin. On the date of her first visit, she was taking clindamycin 300 mg orally three times daily for the cyst-like lesions. She was also applying tretinoin cream to the hyperpigmented areas of her chest once daily and washing with clorhexidine cleanser in the shower. The patient had been treated in the past with various courses of oral cephalexin, doxycycline, minocycline, and trimethoprim-sulfamethoxazole for the hidradenitis suppurativa. In addition, several of the cystic lesions were previously incised and drained, and other lesions were injected with intralesional triamcinolone with minimal long-term resolution. Last year, the patient underwent Fraxel laser resurfacing around the perioral area with no noticeable improvement.

PAST MEDICAL HISTORY

The patient denied any other significant past medical history.

MEDICATIONS

Clindamycin
Tretinoin cream
Omega-3 Fatty Acid
Lactobacillus Rhamnosus Probiotic
Prenatal Vitamin
Ergocalciferol

ALLERGIES

There were no known drug allergies.

FAMILY HISTORY

The patient's mother also reported a 15-20 year history of chest and axillary hyperpigmentation. She acknowledged a similar history of cystic lesions in her axillae and pitting scars in the periorificial area. The patient denied any other additional family members with similar cutaneous findings.

SOCIAL HISTORY

The patient is a current daily smoker. She has been smoking approximately one-half pack of cigarettes daily for over 20 years.

PHYSICAL EXAM

During the initial examination, reticular medium-brown hyperpigmented patches were noted on the mid-chest, inframammary folds, and upper abdomen. Smaller hyperpigmented macules were seen in the bilateral axillae. The patient also had multiple erythematous cystic lesions in the bilateral axillae, along the inframammary areas, and lining the inguinal folds. Small, pitted scars were identified in a perioral distribution.

HISTOPATHOLOGY
A punch biopsy of the right inframammary fold demonstrated a reticulated epidermis with elongated rete ridges and basal melanin pigmentation. The specimen also revealed a folliculo-infundibular cyst. The findings were suggestive of Dowling-Degos disease.

LABORATORY RESULTS
None

DIAGNOSIS
Dowling-Degos disease

TREATMENT AND COURSE
The patient was started on niacinamide 500 mg TID during the initial visit. The patient stated she was most concerned about the hyperpigmentation of her central chest. After her biopsy revealed epidermal hyperpigmentation, she underwent spot testing with various combinations of microlaser peels and fractional laser treatments in the office to target the dyschromia.

DISCUSSION
Dowling-Degos disease is a rare genodermatosis characterized by reticulate hyperpigmentation. Because the disorder is often associated with dark comedone-like lesions, it has also been referred to as “dark dot disease”. The disease is inherited in an autosomal dominant fashion with variable penetrance. Women are more predominantly affected than men in a ratio of 2:1. The disorder is caused by a loss-of-function mutation in the keratin 5 gene. A missense mutation in the same genomic region results in epidermolysis bullosa with mottled pigmentation.

The clinical presentation of Dowling-Degos disease consists of reticulated hyperpigmentation with brown macular and papular lesions. The hyperpigmentation usually begins in the axillae and later progresses to involve the inframammary folds, intergluteal folds, neck, trunk, and medial extremities. Lesions have also been reported on the scalp, neck, and genitalia. The appearance of the lesions is unchanged by sun exposure, and the onset of the pigmentation is typically in the third or fourth decades of life. The lesions are generally asymptomatic, but some patients report mild pruritus in affected flexural areas. Other features of the disease include pitted perioral scars, epidermoid cysts, and comedone-like lesions of the posterior neck. The disorder has been associated with hidradenitis suppurativa and multiple keratoacanthomas likely due to a defect in pilosebaceous epithelial proliferation that predisposes affected individuals to follicular plugging.

On histology, the basal layer will have increased pigmentation and an irregular filiform elongation of the rete ridges, and the suprapapillary epidermis will appear thinned. These features can result in an overall antler-like configuration. The stratum corneum will demonstrate orthokeratosis and hyperkeratosis, and small epidermal keratin cysts can be identified in the epidermis. There is often a lymphohistiocytic infiltrate in the papillary dermis along with pseudo-horn cysts. S100 staining does not reveal an increased population of melanocytes.

Galli-Galli disease is a rare variant condition of Dowling-Degos disease. It is clinically similar to Dowling Degos disease with reticulated hyperpigmentation of the flexures with associated papules. However, on histopathology, the disorder will demonstrate suprabasal focal acantholysis in addition to the elongation of the rete ridges. Galli-Galli is also considered a very pruritic condition, and treatment is unfortunately disappointing.

Several treatments have been tried in patients with Dowling-Degos disease with rare success. Because the disease is due to a genetic defect, treatment regimens are aimed at symptom

relief. Studies have reported use of topical tretinoin, adapalene, hydroquinone, and corticosteroids. A recent study reported success with Er:YAG ablative laser treatment in one patient with reduction of the hyperpigmented papules 2.5 years after treatment.

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CHICAGO DERMATOLOGICAL SOCIETY **CASE # 6**

Presented by Conor Dolehide, MD and Brian Bonish, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A 30-year-old white male presented to the emergency department for fatigue, shortness of breath, weight loss (twenty-five pounds over two months), diarrhea, blurred vision, and widespread skin lesions involving his bilateral upper and lower extremities, groin, torso, and, head. The eruption began two months prior as asymptomatic red and purple lesions in the groin, which then "turned black in the center." The lesions were painful after ulceration.

He had been evaluated one month earlier by another dermatologist. At that time, labs were remarkable for thrombocytopenia (PLT 108) and hyponatremia (Na 128). Punch biopsy for hematoxylin and eosin staining demonstrated a superficial and deep, dense, perivascular and interstitial, atypical, lymphocytic infiltrate. There were scattered necrotic keratinocytes in the epidermis. CD30 was negative. Biopsy for direct immunofluorescence was negative. Culture showed moderate growth of *Acinetobacter lwoffii.* He was started on methotrexate 2.5mg daily (which he took once), light therapy, and he completed one week of trimethoprim/sulfamethaxasole. He was advised to follow up at an academic center for further management.

Three years prior to this presentation, he had developed symptoms which included intermittent fevers and chills, fatigue, and malaise. Symptoms would occur every three to six months and would last for one or two weeks. They were not associated with skin lesions at that time. Notably, he had traveled to Mexico three years prior to this presentation.

PAST MEDICAL HISTORY

No significant history

MEDICATIONS

None

ALLERGIES

None

FAMILY HISTORY

No pertinent family history

SOCIAL HISTORY

He occasionally drank alcohol and he smoked cigarettes daily. He last used cocaine, heroin, and marijuana three years ago. Not sexually active for three years.

PHYSICAL EXAM

On the bilateral upper and lower extremities, torso, and head, there were round, violaceous, and infiltrative nodules and plaques, many with central black eschars and peripheral violaceous rims. There were petechiae on the hard palate. There were erosions and ulcerations of the groin and testes. There was lymphadenopathy of the anterior and posterior neck and injection of the bilateral sclerae.

LABORATORY RESULTS

The following initial labs were positive or abnormal:

Sodium……	115	(normal 137 – 147)
Venous Lactic acid……	6.3	(normal 0.5 – 1.7)

AST……..	238	(normal 3 – 44)
ALT……...	96	(normal 0 – 40)
Fibrinogen……	114	(normal 190 – 395)
Hemoglobin……..……......	10.1	(normal 13.5 – 17.5)
Platelet Count……	.49	(normal 150 – 399)
CPK…….....….	927	(normal 10 – 205)
EBV DNA Quantification……...	259,464	(normal < 250)
Ferritin……..…….....	24,855	(normal 12 – 410)
Lactate Dehydrogenase…….	808	(normal 110 – 240)
Triglycerides……	289	(normal 30 – 149)

T-cell receptor gene rearrangement by PCR and heteroduplex analysis did not show a clonal T-cell receptor gene rearrangement product.

MICROBIOLOGY

Tissue and urine cultures were positive for *Pseudomonas aeruginosa.*

IMAGING

Transthoracic echocardiogram showed a moderate pericardial effusion and marked right ventricular chamber collapse consistent with tamponade physiology.

Computed tomography of the chest demonstrated increased thickness associated with nodularity in the left ventricle consistent with an infiltrative disorder of the myocardium.

Computed tomography of the abdomen and pelvis showed that the spleen was enlarged measuring 13.3 cm in length**,** peri-splenic ascites, and patchy-appearing perfusion of the bilateral kidneys. There was also diffuse wall thickening of the entire colon and small bowel.
Magnetic resonance imaging of the brain showed polypoid mucosal thickening in the maxillary and sphenoid sinuses. There was also mucosal thickening and patchy opacification of the ethmoidal and bilateral mastoid air cells. There were retained secretions in the nasopharynx and oropharynx. There was an enlarged and mildly enhancing right superior rectus muscle.

PATHOLOGY

Punch biopsies from the right and left upper arm demonstrated a moderately dense perivascular and periadnexal infiltrate of highly atypical lymphoid cells with frequent mitotic figures. The angiocentric and adnexocentric atypical lymphoid infiltrate in the dermis stained positive for CD3, CD56, and EBV-encoded RNA (EBER in situ hybridization). Stain for CD10 highlighted the dendritic meshwork.

Bone marrow biopsy showed a mildly hypercellular marrow with trilineage maturation and scattered EBV positive cells.

Bone marrow flow cytometry did not show evidence of lymphoma or an increase in NK cells.

Flow cytometry from the peripheral blood showed that NK cells comprised approximately 35% of the total leukocytes and 84% of the lymphocytes.

DIAGNOSIS

Extranodal NK/T-cell lymphoma, nasal type

TREATMENT AND COURSE

The patient was pancytopenic and febrile by his second day of admission. His dyspnea did not improve after evacuation of his cardiac tamponade. Despite treatments with steroids, pressors, antibiotics, antifungals, and the initiation of chemotherapy with etoposide, the patient continued to decline and passed away. The autopsy revealed a gastric perforation, ascites, and *Candida albicans* infection of the lung and serosal surfaces, as well as disseminated lymphoma in the skin, heart, lungs, stomach, liver, spleen, testes, bone marrow, and lymph nodes.

DISCUSSION

In 1987, markers of natural killer (NK) cells were found in nasal and paranasal lymphomas. Further studies of similar tumors confirmed the presence of this marker—the neural crest adhesion molecule, (NCAM) or CD56. When NK lymphomas occur as nasal masses or destructive midline facial lesions, they are termed nasal NK/T-cell lymphomas. An identical tumor arising in an extranasal site is classified as an extranodal NK/T-cell lymphoma, nasal type. Some of the extranasal sites include the aerodigestive tract, skin, soft tissue, gastrointestinal tract, lungs, spleen, eye, brain, and testes. The skin is the second most common site of involvement after the nasopharynx. When the skin is involved, it is generally an aggressive neoplasm, and the patient may be unaware of extracutaneous disease.

It is a rare lymphoma, which is much more common in Asia, South America, and Central American than in Europe and North America. In a multination study of 129 cases of extranodal NK/T cell lymphomas, Asians accounted for 80% of the nasal cases and 84% of the extranasal cases, while Caucasians accounted for only 9% of the nasal and 13% of the extranasal cases. EBV is highly associated with the disease, although lower EBV infection rates have been described in the United States. It is also commonly associated with hemophagocytic lymphohistiocytosis (HLH) or hemophagocytic syndrome, which usually follows a rapidly fatal course. To diagnose HLH, patients must have a molecular diagnosis consistent with HLH or fulfill five of eight diagnostic categories including fever, splenomegaly, ferritin ≥500 μg/L, soluble CD25 (IL-2 receptor) ≥2,400 U/ml, low or absent NK-cell activity, cytopenias (≥2 of 3 lineages in the peripheral blood), hypertriglyceridemia and/or hypofibrinogenemia, and hemophagocytosis in bone marrow, spleen, or lymph nodes.

Microscopically, there are inflammatory cells, atypical cells of varying sizes, and mitoses. The tumor cells are often angiocentric. They can infiltrate and destroy the blood vessel walls. Zonal necrosis is a consistent feature. There may be epidermotropism. Immunohistochemistry usually shows surface CD3–, cytoplasmic CD3e+, CD56+, TIA-1+, perforin+, and granzyme B+. Diagnosis often requires in situ hybridization of EBV using probes for EBV encoded RNA (EBER). Clonal T cell receptor (TCR) gene rearrangements can occur, but are usually negative.

This case illustrates a thirty-year old Caucasian male in the United States who presented with primarily cutaneous involvement of an extranodal NK/T-cell lymphoma, nasal type as well as hemophagocytic syndrome.

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Presented by Bryan Sofen, MD, Michael Tharp, MD, and Warren Piette, MD
Department of Dermatology, RUSH University Medical Center

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 8**

Presented by Conor Dolehide, MD and James Ertle, MD
Department of Dermatology, RUSH University Medical Center

HISTORY OF PRESENT ILLNESS

A fifteen-year-old male presented with acne and facial swelling for two years. A photograph from his eighth grade graduation confirmed the absence of facial edema or lesions prior to his first presentation. He reported minimal improvement with one year of oral and topical antibiotics, tretinoin cream, and benzoyl peroxide. He was otherwise healthy. A review of systems was unremarkable.

PAST MEDICAL AND SURGICAL HISTORY

None relevant.

MEDICATIONS

Doxycycline 100mg twice daily
Tretinoin 0.1% cream nightly
Clindamycin 1% solution daily
Benzoyl peroxide 5% gel daily

ALLERGIES

No known drug allergies.

FAMILY HISTORY

None relevant.

SOCIAL HISTORY

Lives with family.

PHYSICAL EXAM

There were acneiform papules and cysts predominantly on the central face including the chin, nose, malar cheeks, and glabella. There was also non-pitting, non-tender, firm edema of the upper face.

HISTOPATHOLOGY

Shave and punch biopsies for hematoxylin and eosin staining showed periadnexal and perivascular lymphocytic inflammation, as well as dermal fibrosis. Lymphatic endothelium stained with D2-40.

DIAGNOSIS

Morbihan's disease (Solid facial edema)

TREATMENT AND COURSE

The patient completed six months of isotretinoin (40 mg twice daily) with improvement of both the edema and acneiform papules. The edema continued to improve with two months of oral prednisone tapers (40 mg x 1 week, 30 mg x 1 week, 20 mg x 1 week, 10 mg x 1 week). He was continued on prednisone 10mg daily. Intralesional triamcinolone (2.5-5 mg/cc) improved the remaining scars and cysts. He continues to have edema of the upper face.

DISCUSSION

In 1957, French dermatologist, Robert Degos observed chronic persistent edema and erythema of the upper face in a French farmer who came from the region of Morbihan (North-Western France). In 1991, Gorin, *et al.* designated this syndrome as Morbihan's disease. It is also known as lymphedematous rosacea or solid facial edema.

Morbihan's disease is a complication of acne vulgaris or rosacea. It is characterized by slowly accumulating solid edema of the upper face, including the forehead, glabella, eyelids, and cheeks. It may present at any stage of acne or rosacea. It is asymptomatic, although the periorbital edema may impair vision.

The pathogenesis is unknown. One hypothesis is that perilymphatic granulomas and intralymphatic histiocytes cause lymphatic obstruction. Another hypothesis is that chronic inflammation leads to the destruction of connective tissue around dermal vessels resulting in exudation of fluids and dilatation of the lymphatic vessels.

Histopathology is nonspecific. There may be dermal edema, perivascular and periadnexal lympho-histiocytic inflammation, granulomas, sebaceous hyperplasia, and/or dilated lymphatic vessels.

The edema will not resolve without intervention. However, even with intervention, it is often refractory to treatment. The most effective treatment seems to be isotretinoin. Other treatment options include systemic glucocorticoids, ketotifen, and clofazimine. CO2 laser blepharoplasty has been reported in one patient. Treatments such as antibiotics, lymphatic massage, irradiation, interferon gamma injections, thalidomide, and antihistamines seem to be ineffective.

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Fast Break #2

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 9**

Presented by Blake Troiani, MD and Arthur Rhodes, MD
Department of Dermatology, RUSH University Medical Center

Unknown

CHICAGO DERMATOLOGICAL SOCIETY **CASE # 10**

Presented by Bryan Sofen, MD, Mark Hoffman, MD, and Arthur Rhodes, MD
Department of Dermatology, RUSH University Medical Center

CASE A

HISTORY OF PRESENT ILLNESS

A 25-year-old white man presented with a 3-day history of malaise, arthralgias and myalgias (greatest in his left foot), dizziness, headaches, fever, chills, night sweats, and neck stiffness. The problems began with a severe sharp pain at the ball of his left foot, associated with numbness and tingling of the plantar surface. Two days later, he developed a painful eruption on his bilateral palms and plantar feet, associated with diffuse arthralgias and myalgias. Two weeks prior to presentation, he had nasal congestion, sore throat, and a productive cough. There was also new-onset blurred vision in left eye, which was first noted during our examination. He denied photophobia or eye pain. He denied recent travel, hiking, or camping.

The patient works as a bartender/bar manager and his workplace had undergone recent construction. He denied recent travel, but moved to Chicago from Arizona in May of 2013. He also denied sick contacts, penile discharge, or genital lesions. He has been sexually active with a single partner. His most recent sexually transmitted disease screening was approximately 6 months prior, negative per patient.

PAST MEDICAL HISTORY

Nephrotic syndrome as a child
Chlamydia several years ago
Motor Vehicle Accident 1 year ago, hospitalized after sustaining multiple fractures of ribs and right leg

MEDICATIONS, ALLERGIES, & FAMILY HISTORY

None Relevant

SOCIAL HISTORY

Denied use of illicit drugs
Admits to smoking cigarettes and moderate consumption of alcohol.

PHYSICAL EXAM

Upper chest/face: diffuse, mild macular erythema
Upper/lower extremities, mostly acral: scattered dull red papules and pustules/vesiculopustules [some hemorrhagic] on an erythematous base; no obvious purpura
Left eye: scleral injection
Fingernails: splinter hemorrhages evident; no periungal telangiectasias. no papules or nodules on palms or fingertips
No livedo reticularis; no dermal nodules anywhere
Oral mucosa and genitalia: normal
No cervical, axillary, or inguinal lymphadenopathy
No hepatosplenomegaly

HISTOPATHOLOGY

Punch biopsy, left knee papule: Mild superficial perivascular dermatitis with changes of lichen simplex chronicus and dermal hemorrhage.

LABORATORY RESULTS
CBC: remarkable for WBC 16,000/ml
INR: 1.4
ESR 12 mm/hr.
CRP 258 (0.0 – 8.0 MG/L) and CK 341 (10 – 205 U/L)
AST/ALT 79/118
Cocaine metabolite and opiate: both positive on toxicology screen
C3 and C4 normal.
Anti-dsDNA: 40 IU/ML (>33 IU/ML is positive).
Blood cultures +Methicillin-resistant *Staphylococcus aureus*
Tissue Culture: negative for aerobes, anaerobes, Acid Fast Bacilli, and fungi

IMAGING
Chest X-Ray: No acute cardiopulmonary process.
CT of brain: Unremarkable
Lumbar puncture: Normal
Transthoracic echocardiogram: No diagnostic evidence for valvular vegetation.
Transesophageal echocardiogram: Mitral valve showed marked, holosystolic prolapse with a valvular vegetation. There was severe regurgitation on Doppler.
MRI of brain: Multiple scattered foci of restricted diffusion, consistent with multiple subacute embolic infarcts of varying ages.
MR angiogram: Unremarkable, No evidence of mycotic aneurysms.

DIAGNOSIS
Acute bacterial endocarditis with septic emboli

TREATMENT AND COURSE
The patient underwent mitral valve repair and Medtronic mitral band placement. He was discharged on vancomycin 1750 mg q8h and rifampin 300 mg q12h for 6 weeks. He is doing well and all cutaneous lesions have resolved.

CASE B

HISTORY OF PRESENT ILLNESS
A 52-year-old white male presented with a 3-month history of fatigue and purpuric lesions, initially around his ankles, slowly progressing to involve a stocking-glove distribution over his hands and feet. Individual lesions were asymptomatic except for occasional leg pain. The patient had been treated for infectious endocarditis secondary to *Streptococcus viridans* in 2012, complicated by a left middle cerebral artery ischemic stroke and subarachnoid hemorrhage related to mycotic aneurysms, requiring craniotomy and ventriculoperitoneal shunt. He did not undergo valve repair at that time because of the cranial pathology. A transthoracic echocardiogram during his present admission showed severe aortic regurgitation with a strong likelihood of valvular vegetation. He was admitted with a diagnosis of presumed recurrent bacterial endocarditis.

A review of systems was negative for nausea, vomiting, diarrhea, constipation, chest pain, dyspnea, and cough. The only new medication was ciprofloxacin for a urinary tract infection recently diagnosed by his primary care physician. This medication was started after the onset of symptoms. He denied any sick contacts.

PAST MEDICAL HISTORY
Infective Endocarditis (*Streptococcus viridans*)

Ischemic Stroke
Subarachnoid hemorrhage
Hypertension
Hydrocephalus

MEDICATIONS
Ciprofloxacin
Ceftriaxone
Acetaminophen
Levetiracetam (Keppra)
Fluoxetine (Prozac)

ALLERGIES
Augmentin

FAMILY HISTORY
Paternal grandfather - stroke, mother - diabetes

SOCIAL HISTORY
Former smoker, quit in 1983, 5 pack year history.
Married. Lives with family, who act as his caretakers since his cerebrovascular accident. Retired salesman. No longer employed after cerebrovascular accident

PHYSICAL EXAM
Splinter hemorrhages on nail beds left thumb, right 4th finger, right 2nd toe, and right 4th toe
Bilateral lower extremities (extending up to groin)/bilateral upper extremities: Numerous erythematous and purpuric macules and minimally raised papules, 1-4 mm in diameter, up to 0.5 mm in height; few with a central hemorrhagic crust. Lesions most prominent in a dependent, stocking-glove distribution, over hands and feet
No palmoplantar lesions
No Janeway lesions or Osler's nodes
No petechiae seen in oral mucosa or conjunctivae

HISTOPATHOLOGY
Punch Biopsy x 2, left medial thigh, H&E: leukocytoclastic vasculitis, no vascular emboli identified. The pathology was thought not to be suggestive of septic vasculitis.

LABORATORY RESULTS
CBC, CMP WNL
Urinalysis: positive for blood and leukocyte esterase
Blood Culture positive for *Enterococcus faecalis*
Tissue Culture: Negative for bacteria, fungi, and acid fast bacilli.

IMAGING
Transthoracic echocardiogram: Severe aortic regurgitation, with 17 x 9 mm highly mobile, pedunculated vegetation. Mild mitral valve regurgitation, with 3 x 4 mm vegetation.
CT scan of Brain: Left hemispheric encephelomalacia, associated with volume loss. The ventriculoperitoneal shunt was unremarkable.

DIAGNOSIS
Recurrent bacterial endocarditis presenting with leukocytoclastic vasculitis

TREATMENT AND COURSE
This patient underwent an aortic and mitral valve replacement, complicated by postoperative pneumothorax the next day, relieved by a chest tube. He was discharged with a peripherally inserted central catheter and a 1 month course of Ceftriaxone 2g IV q12 and ampicillin 2g IV q4H. The leukocytoclastic vasculitis subsequently resolved following treatment of the underlying endocarditis and surgical replacement of both his mitral and aortic valve.

DISCUSSION
There are several forms of endocarditis, causing numerous cutaneous findings. Non-bacterial thrombotic endocarditis (NBTE), formerly known as marantic endocarditis, represents sterile, focal vegetations composed of fibrin, platelets, and/or immune complexes deposited on valve leaflets. NBTE is associated with systemic lupus erythematosus (Libman-Sacks endocarditis or anti-phospholipid associated), solid tumor malignancies (particularly mucinous adenocarcinomas), and hypercoagulable states due to other causes. In contrast, infective endocarditis involves larger, more inflammatory vegetations composed of numerous varieties of bacteria. *Streptococcus spp.* (especially *S. viridans*) cause the majority of valvular endocarditis cases, whereas *Staphylococcus spp.* (especially *S. aureus*) is the primary agent in intravenous drug abusers. Acute endocarditis presents with the rapid onset of symptoms following valvular colonization, as quickly as 2 weeks, whereas symptoms develop over weeks to months in subacute bacterial endocarditis.

Case A illustrates many of the classic findings of infective endocarditis, contrasted with those of Case B, in which leukocytoclastic vasculitis emerged as a presenting sign of recurrent bacterial endocarditis. The cutaneous manifestations of all forms of endocarditis are caused by emboli. In acute infective and septic endocarditis, the emboli are loose bacterial vegetations that have broken free from the primary foci on a cardiac valve. In contrast, the emboli in non-bacterial or subacute bacterial endocarditis represent immune complexes deposited in the peripheral vasculature. Bacterial emboli may manifest as small, hemorrhagic or grayish vesciulopustules. Gram positive septicemia is more likely to result in generalized, diffuse erythema, widespread petechial or purpuric lesions, and splinter hemorrhages of the nail beds. Osler's nodes are tender, red/purple papules and/or nodules of volar surfaces of the hands and feet caused by immune complex deposition, which also cause the retinal hemorrhages known as Roth spots. In contrast, Janeway lesions are small, non-tender hemorrhagic palmoplantar macules, nodules, or microabscesses caused by true septic emboli, more often associated with overlying necrosis. As in Case A, the most common presenting symptom of streptococcal sepsis is severe pain in an extremity with or without underlying soft tissue infection.

Leukocytoclastic vasculitis (LCV) may be the presenting sign of infective endocarditis, with some studies showing LCV occurring in 3.6% of patients with infective endocarditis. In Case B, LCV was a harbinger of recurrent endocarditis. Interestingly, LCV secondary to infective endocarditis is commonly associated with disease caused by intestinal, oral, or genital flora rather than skin flora, i.e. *Enterococcus faecalis* in our patient and *Granulicatella species* in other patients. Notably, the Case B patient did not have LCV with his original course of endocarditis caused by *S. viridans*. In subacute bacterial endocarditis, purupura is actually the most commonly reported skin finding.

Regarding the diagnosis of endocarditis, transthoracic echocardiogram (TTE) has a relatively low sensitivity (29-63% in different series) but a high specificity (approaching 100%). TTE and transesophageal echocardiograms (TEE) can be falsely negative if vegetations are small (as in Libman-Sacks non-bacterial endocarditis), or if previously present loose vegetations have

embolized. Serial blood cultures are mandatory to monitor recurrence during and following antibiotic therapy. Cutaneous findings resolve with treatment of the underlying infection.

These two cases are presented to illustrate the variable cutaneous presentations of endocarditis. It is important to keep endocarditis in mind in any new unexplained cases of LCV or with any findings typical of septic vasculitis.

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Presented by Andrew Nesterovitch, MD and Arthur Rhodes, MD, MPH
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HISTORY OF PRESENT ILLNESS

A 4-year-old light-skinned Hispanic male presented with a 1-year history of brown asymptomatic spots on the face and torso. The first lesions appeared periorally. The parents denied any intraoral lesions in the child. The patient's growth and development have been normal. He sees a speech therapist, but is otherwise meeting developmental milestones. He does not have any heart valve disease, cardiac arrhythmias, vision abnormalities, hearing problems or growth abnormalities. He has no history of other skin disorders, skin cancers, melanoma, or other malignancies.

PAST MEDICAL HISTORY

No pertinent past medical history

MEDICATIONS

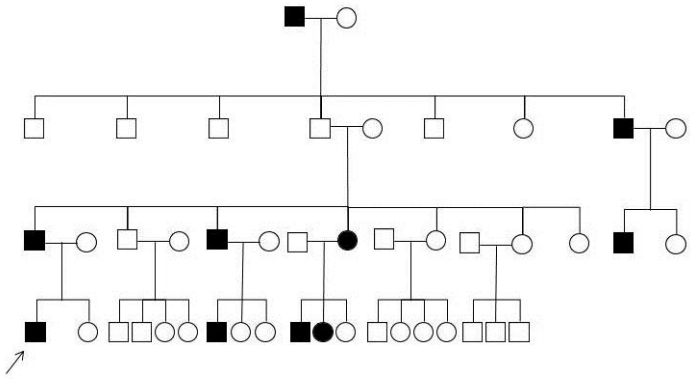
None

ALLERGIES

None

FAMILY HISTORY

Similar asymptomatic pigmented lesions have been noted in 9 blood relatives out of 36 on paternal side of the family (great grandfather, grandfather's brother and his son, father and his one brother and one sister, and their children (3 nephews of patient). See family tree.



Family medical history revealed no heart valve diseases, cardiac arrhythmias, vision abnormalities, hearing problems, mental disorders or growth/skeletal abnormalities. There is no family history of early or sudden death. There is no family history of skin cancers, melanoma, or other malignancies.

PHYSICAL EXAMINATION

The child is well developed, overweight, and interactive. Face, chest, abdomen, thighs, legs, buttocks, and back revealed dozens of light to medium brown macules. Pinpoint blue-brown macules were evident on the bilateral conjunctivae. There were no oral mucosal. There were no lesions on the vermillion of the lips, genitalia or anus.
The patient's father was examined. Evident were uncountable and densely populated medium brown macules involving his face, torso anterior and posterior, extremities, vermillion lips and

genitalia (penis, scrotum, anus). There were no intraoral mucosal lesions. There were no palmar or plantar lesions.

HISTOPATHOLOGY

Normal skin from back, site A: Unremarkable skin with elongated rete ridges. Brown macule from back, site B: consistent with lentigo simplex. In comparison with normal skin, this brown macule reveals prominent melanin basal pigmentation and pronounced elongated rete ridges.

DIAGNOSIS

Familial generalized lentiginosis.

DISCUSSION

Generalized lentiginosis (GL) is a rare familial or sporadic condition that is characterized by widespread lentigines without associated somatic abnormalities. The lentigines develop early in life and slowly increase in number on the face, torso, extremities, and genitalia. The buccal mucosa, conjunctivae, palms, and plantar surfaces are usually spared.

GL must be differentiated from familial lentiginosis syndromes that are associated with somatic abnormalities, including potentially serious internal organ disease. In the absence of mucosal involvement, GL must be differentiated from LEOPARD syndrome (multiple Lentigines with Electrocardiographic conduction defects, Ocular hypertelorism, Pulmonary stenosis, Abnormalities of genitalia, Retardation of growth, and Deafness). Familial GL and LEOPARD syndrome are inherited in an autosomal dominant manner. LEOPARD syndrome patients have a mutation in the PTPN11 gene (12q24.1 gene locus) or RAF1 gene (3p25). In contrast to GL, the lentigines in LEOPARD syndrome often occur on palms and plantar surfaces. A review of almost 40 reports of LEOPARD syndrome demonstrated lentigines in 100% of patients, EKG abnormalities and cardiac murmurs in 80%, skeletal abnormalities in 60% (including small stature in 42%), hypertelorism in 50%, mental retardation in 35%, abnormal genitalia (males) in 29%, and sensorineural deafness in 27%. Some of these features did not become clinically manifest until puberty.

For our patient presented herein, the absence of a family history of internal organ abnormalities within several generations strongly suggests a diagnosis of GL. In sporadic cases of GL, and in cases with small numbers of family members, one needs to consider cardiology, ophthalmology, urology and audiology evaluations.

In the presence of mucosal involvement, wide spread lentigines may be the first indication of LAMB syndrome (Lentigines, Atrial myxoma, Mucocutaneous myxoma, Blue nevi), subsequently popularized as Carney complex. This syndrome has been associated with an autosomal dominant mutation in the PRKAR1A gene (17q22-24 gene locus).

Other familial lentiginosis syndromes have been associated with localized multiple lentigines. These syndromes must be considered in the differential diagnosis of GL, LEOPARD and LAMB/Carney complex. During the onset of those syndromes, lentigines present in a localized manner and slowly increase in number. Mucosal involvement (in contrast with GL and LEOPARD) might suggest the diagnosis of Peutz-Jeghers syndrome (LKB1/STK11 gene on chromosome 19p13.3) with associated small intestinal polyposis and malignant neoplasias of the gastrointesinal tract, pancreas, breast, ovary and uterus. Lentigines of the lips, oral mucosa, acral surfaces, genitalia, and nail beds have been reported in Laugier-Hunziker syndrome. Cowden syndrome (PTEN gene, 10q23.31, associated with macrocephaly, lipomatosis, mental retardation and vascular malformations) may present with multiple localized periorificial and acral lentigines.

Of note, a newly discovered gene locus on chromosome 4q21.1-q22.3 in one GL family may be useful in the diagnosis of familial GL, but confirmatory studies are needed.

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Presented by Andrew B. Nesterovitch, MD and Mark Hoffman, MD
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HISTORY OF PRESENT ILLNESS

A 57-year-old white man presented for skin lesions on his left arm and left thigh for 4 months.

The patient had traveled to Varese, Italy 6 months prior to presentation, where he experienced "bug bites" on his left upper arm while hiking; the lesions lasted for weeks and then resolved. The following month found him in Rio Claro, Brazil, where he reports also having sustained arthropod bites. Skin lesions recurred on the arm and appeared on his thigh 1 month later, following his return to the US.

A few weeks prior to our evaluation the patient consulted dermatology at the Mayo clinic, where a biopsy was consistent with leishmaniasis. He presented to Rush for further evaluation and potential treatment.

PAST MEDICAL HISTORY

Thrombocytopenia, HTN, hyperlipidemia, hypothyroidism, glaucoma, tubular adenoma of colon

MEDICATIONS

Atenolol
Lisinopril
Levothyroxine
Latanoprost
Timolol solution

SOCIAL HISTORY

Frequent world travel for work (India, China, Italy, Brazil) marketing washing machines

PHYSICAL EXAM

Left dorsal proximal forearm: 8 pink to violaceous papules, some with central crusting, some clustered; none ulcerative.
Left upper thigh: 2 violaceous papules and 1 plaque (largest 1.0 x 1.0cm); plaque with central ulceration (possibly from biopsy dehiscence) and crust.
Oral mucosa clear. No axillary or inguinal lymphadenopathy

HISTOPATHOLOGY

Skin biopsy of left arm (A), and left thigh (B) at Mayo clinic (2/20/2013). The epidermis is ulcerated. Within the dermis, there is dense mixed inflammatory infiltrate composed of granulomas, plasma cells, histiocytes, and lymphocytes. Intracellular organisms with a suggestion of kinetoplasts are present in histiocytes. The organisms are relatively numerous in specimen B [left thigh] on H&E, Gram, Giemsa stains. The organisms are more focal and subtle in specimen A [left arm], and are focally visualized (Giemsa stain). AFB stain, Treponema pallidum immunostain, PAS stain, and GMS stain are negative. Left arm: Suggestive of leishmaniasis. Left thigh: Leishmaniasis. [David J. DiCaudo, M.D.]

The same slides were reviewed at Rush (3/6/2013): Sections show surface ulceration and granulomatous inflammation in underlying dermis. Close to the ulcerated surface there are intracellular organisms consistent with leishmania. The organisms are most numerous and easily visible in the specimen from left thigh (part B.) and rather subtle in specimen from left arm (part A). Left arm (A): Consistent with leishmaniasis. Left thigh (B): Leishmaniasis. [Vijaya Reddy, M.D.]

Skin biopsy of left dorsal forearm at Rush (3/6/2013): Granulomatous Dermatitis (dense mixed inflammatory infiltrate composed of granulomas, plasma cells, histiocytes, and lymphocytes in the dermis). The definite organisms are not seen on PAS, Giemsa and GMS stains, the biopsy finding are consistent with leishmaniasis. [Lady C. Dy, M.D]

LABORATORY RESULTS

Indirect fluorecent antibody (CDC): positive *L. donovani* complex, titer 1:32
Leishmania PCR (CDC, 3/8/13): *L. dononovani* complex positive (*L. donovani/chagasi/infuntum*)
PLT 125; WBC, RBC, Hgb, Hct, Alk Phos, AST WNL

DIAGNOSIS

Cutaneous leishmaniasis due to *Leishmania infantum/chagasi.*

TREATMENT AND COURSE

Fluconazole 200 mg daily for 6 weeks with complete clinical resolution

DISCUSSION

The protozoan parasites of the genus *Leishmania* can cause three major clinical forms of disease: 1) cutaneous leishmaniasis (CL); 2) mucocutaneous leishmaniasis (MCL); and 3) visceral leishmaniasis (VL) [Kala-azar "Black fever"]. Transmission occurs via sandflies, primarily of the generae *Phlebotomus* (Old World) and *Lutzomyia* (New World).

Leishmania species from the *Leishmania donovani* complex (*L. donovani* and *L.infantum/chagasi*) are well known to cause visceral leishmaniasis. *L. donovani* and *L. infantum/chagasi* can also cause skin-limited cutaneous leishmaniasis (CL).

The initial lesion of CL is a small erythematous papule. The papule slowly increases in size and forms a nodule or a plaque that may ulcerate with raised violaceous borders and become covered with an exudate or dry central crust. Usually the CL ulcers are not painful (unless secondary infected). The lesions may show a variable degree of polymorphism. Four main clinical forms have been proposed by Rioux et al. (1985): 1) ulcerative, 2) papulous, 3) impetiginoid, and 4) infiltrative. CL also can present as psoriasiform or verrucous plaques, and sporotrichoid lesions in cases of lymphatic spread.

The MON (for Montpellier, France) classification system, based on multilocus enzyme electrophoresis (MLEE) has been developed for typing of the different *Leishmania* strains (zymodemes). Approximately 2061 samples of *L. infantum* have been described and collected over the last 40 years: 1166 samples from human hosts (56.6%): 901 with VL and 242 with CL. The *Leishmania spp.* from a lesion aspirate or skin biopsy are usually cultured in Nicolle-Novy-MacNeal media. Special arrangements have to be made for collection and shipping of skin biopsy specimens to the CDC for diagnostic testing. Currently, the CDC uses DNA PCR technology for *Leishmania species* identification that cannot distinguish the species within the *L. donovani* complex. The definition of *L. donovani donovani* or *L. donovani infantum/chagasi* species are based of epidemiologic and geographic criteria. No current test can distinguish between dermotropic strains and viscerotropic strains *of L. infantum/chagasi*. Both parasite and host characteristics are important in determination of visceralization. Several studies have found that factors such as species-specific gene polymorphisms, pseudogenes, copy number variations, expression level for virulence and stress response genes, resistance to higher visceral temperatures, different phosphorylation profile, number of inoculated parasites, level of vasodilatation during inoculation, pre-exposure and sensitization to the sandfly saliva, immunocompetence of a host can all contribute to differences in disease pathology.

If untreated, most cases of localized cutaneous leishmaniasis resolve spontaneously, usually after 1 year, but they can take as many as 3 years to resolve.

Of note, our patient had potential exposures in two endemic areas (Italy and Brazil) within the incubation period of 1-2 months and thus the country of acquisition is uncertain.

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