Case #1

PRESENTED BY: *Lisa Kates, M.D. and Gina Dillig, M.D.*

HISTORY OF PRESENT ILLNESS:

This 48-year-old female presents with persistent redness and flushing of her face. She has had the condition for over 5 years and has recently noticed the appearance of multiple small blood vessels over her cheeks. She has used oral antibiotics and topical metrogel for the past 3 years without any improvement. The patient notes dry eyes on occasion.

PAST MEDICAL HISTORY:

Hypertension

MEDICATIONS:

Hydrochlorathiazide
Doxycycline
Metronidazole
Sunscreen SPF 30

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

The patient has central facial erythema involving the cheeks, forehead and chin. Numerous visible telangiectasias course along the cheeks and nose. No papules, pustules or rhinophymatous changes are appreciated. Her upper chest shows diffuse erythema as well.

LABORATORY EXAMINATION:

The following were negative or normal:
- Complete Blood count
- General Chemistry
- Thyroid function tests
- ANA

BIOPSY:

No biopsy was performed.

DIAGNOSIS:

Erythematotelangiectatic Rosacea

TREATMENT AND COURSE:

The patient was treated December 16, 2004 with the V-Beam 595 pulsed dye laser in a split face model for comparison. We used purpuric settings on the right face with a fluence of 6 J/cm², 1.5 ms pulse duration and a 10 mm spot size. A fluence of 7 J/cm² was used on the visible vessels with the same pulse duration and spot size. There was no more than a 10% pulse overlap to minimize the risk of extensive injury.

We used sub-purpuric settings to the left face at a fluence of 7 J/cm², 10 ms pulse duration with a 10mm spot size and a 50% overlap of pulses. Stacked pulses were used at the visible vessels until purpura was seen (approximately 3 pulses per site). The patient tolerated the procedure well but noted more pain with the treatment on the left side of the face. Ice packs were applied immediately following the procedure and 60 mg intramuscular triamcinolone was administered. Bacitracin ointment was applied to the treated area.

Six weeks after the procedure, improvement in erythema was greater on the right face when compared to the left face. Most linear telangiectasias improved significantly or resolved. The patient will be re-treated in a similar fashion on February 24, 2005.

DISCUSSION:

Rosacea is a common condition characterized by transient or persistent central facial erythema, visible blood vessels and often papules and pustules affecting the facial convexities in a symmetric distribution. The pathogenesis is not completely understood, however several hypotheses have been documented in the literature including the role of vascular abnormalities, dermal matrix degeneration, environmental factors and microorganisms such as *Demodex*

follicularum and *Helicobacter pylori*. Recently, patterns of physical findings have allowed the classification of rosacea into four subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. Indicating the subtype of rosacea is of paramount importance as the pathophysiologic mechanisms and the treatment strategies differ.

The erythematotelangiectatic type of rosacea (ETR) has the characteristic persistent central facial flushing of the face, but the redness may also involve the peripheral face, the ears, the neck or the upper part of the chest. Stimuli known to exacerbate flushing include emotional stress, hot drinks, alcohol, spicy foods, exercise, cold or hot weather or hot baths or showers. There is sparing of the periocular skin. Patients with ETR have a lower threshold for irritation from topically applied substances. They experience stinging and burning that can be quite severe. The skin is usually fine in texture without sebaceous quality or oiliness. There is usually no history of acne and papules and pustules are absent.

Treatment of the ETR includes use of a broad-spectrum sunscreen applied daily. Protective ingredients such as silicones should be included to minimize stinging and erythema in all cosmetic preparations. In the form of dimethicone or cyclomethicone, silicones are nonirritating and nonacnegenic occlusive agents that retard transepidermal water loss. Other key treatment options include topical anti-inflammatory products such as metronidazole or sodium sulfacetamide-sulfur, topical retinoids and oral antibacterial agents or isotretinoin. For those patients that do not respond to topical therapy, cannot tolerate it or prefer a surgical approach intense pulsed light or laser interventions may be selected.

Laser and light therapy for rosacea has been used for the past 20 years. The pulsed-dye laser (PDL) has been proven to be safe and effective in the treatment of a variety of vascular lesions including fine telangiectasias and diffuse erythema. The traditional PDL selectively targets vascular structure through selective light absorption by oxyhemoglobin at 585-595nm and a pulse duration of 0.45 or 1.5ms that prevents damage to the epidermis and surrounding dermis. Acceptance of the laser has been limited due to post-treatment purpura that may persist for up to 2 weeks and associated pain. Recently, modified variable-pulse pulsed-dye laser devices like the 595nm V-Beam can deliver high fluences, 3-25 J/cm², over a much longer pulse duration, 1.5-40ms, allowing minimal post-treatment purpura. The slower heating exceeds the thermal relaxation time of the target vessel, vessels are thermally damaged without undergoing rupture and the extravasation of blood that results in purpura. Additionally, a cryogen cooling spray was developed on the V-Beam to decrease pain and enhance the safety and efficacy of the longer pulsed PDL.

In a study by Alam et al, eleven patients were treated once in a split face model with the V-Beam laser with and without purpura on either side of the face. Each side used 10ms pulse duration and a 7 mm spot size. The fluence was then adjusted to induce purpura on one side and ranged from 8.5-10 J/cm^2. He found that although facial telangiectasias improve with the purpura-free treatment, they improve more after purpura is induced. Fine telangiectasias respond to both treatments, but the purpura-level treatments have a distinct advantage for thicker telangiectasias. Jasim et al demonstrated efficacy with V-Beam at subpurpuric doses, but there was no comparison with purpuric doses. The purpura-free treatments are not without adverse side effects. Clinically significant erythema, edema and discomfort may develop when greater than 250 pulses are used in one treatment session. These undesired effects are less with the purpura-free treatments compared with purpura-inducing treatments and are also less for purpura-free

treatments less than 250 pulses.

When treating superficial telangiectasias with the long pulsed pulsed-dye laser, stacked pulses may allow increased vessel heating using a lower frequency and inturn minimize purpura. A study was done to compare 25 patients treated with single pulses on one side of the face and stacked pulses on the other. The single pulse was adjusted to be just under the purpura threshold and the opposite side used the same settings but stacked 3 or 4 pulses at a repetition of 1.5 Hz until the vessel was no longer visible. The stacked pulses resulted in more pain, edema and erythema, but were more effective and resulted in more vessel clearing as compared to the single pulse. Neither treatment induced purpura.

The optimal treatment for the erythema and telangiectasias of rosacea remains to be elucidated. The long pulse pulsed-dye laser has been proven to be safe and effective without long-term scarring or pigmentary changes. The V-Beam allows parameters to be adjusted for purpuric or subpurpuric settings with single or stacked pulses to achieve the end result of dissipation of telangiectasias and erythema in patients with ETR.

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Case #2

PRESENTED BY: *Warren W. Piette, M.D. and Gina Dillig, M.D.*

HISTORY OF PRESENT ILLNESS:

This 19-year-old female was admitted for a three-day history of a rash on her legs associated with fever, diarrhea and dizziness. She notes that the lesions have increased in number and the individual lesions have increased in size. There is associated pain. She denies abdominal pain and weight loss, although she does describe joint pain and a decrease in appetite. She has had similar lesions in the past, but never this extensive or this painful.

PAST MEDICAL HISTORY:

Autoimmune hepatitis
Spontaneous abortion one week ago

MEDICATIONS:

Prednisone
Azathioprine

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

There were non-blanching slightly palpable retiform purpura ranging from 5 mm-4 cm concentrated below the knees with the left leg more involved than the right. The centers of the larger lesions were dusky red to black, suggesting very early superficial necrosis. Classical

slightly blanching palpable purpura 5 mm or less in size were interspersed among the retiform lesions. The dorsalis pedis and posterior tibialis arteries were palpable bilaterally. The larger lesions were warm to the touch and tender.

LABORATORY EXAMINATION:

The following tests were negative or normal:

- Recommended by our team:
  - General Chemistry
  - Platelet count
  - Aspartate aminotransferase
  - Alanine aminotransferase
  - Rheumatoid factor
  - Cryoglobulins
  - Hepatitis B
  - Hepatitis C
- Ordered by primary service:
  - Factor V Leiden
  - Factors IX, X, XI, XII, XIII
  - Anti-nuclear Antibody
  - Anti-centromere Antibody
  - Anti-mitochondrial Antibody
  - Prothrombin time
  - HIV

The following tests were positive or abnormal:

- Recommended by our team:
  - White blood count 28 k/μL (3.7-10.5 k/μL)
  - Hemoglobin 8.8 g/dL (12.6-16.8 g/dL)
  - BUN 36 mg/dL (8-20 mg/dL)
  - Creatinine 1.8 mg/dL (0.6-1.4 mg/dL)
  - Urinalysis large blood and trace protein
  - Total Bilirubin 2.3 mg/dL (.2-1.2 mg/dL)
  - Direct Bilirubin 1.2 mg/dL (0-.2 mg/dL)
  - Alkaline Phosphatase 32 U/L (50-120 U/L)
  - Lupus Anticoagulant positive
- Ordered by primary service:
  - Lactate dehydrogenase 384 U/L (85-210 U/L)
  - Fibrinogen 54 mg/dL (162-450 mg/dL)
  - D-Dimer 2.81 μg/ml (0-.31 μg/ml)
  - C-Reactive protein 1.23 mg/dL (0-0.09 mg/dL)
  - Erythrocyte Sedimentation Rate 115 mm/hr (0-15 mm/hr)
  - C3 41 mg/dL (88-201 mg/dL)
  - C4 <5 mg/dL (16-47 mg/dL)
  - Haptoglobin 6 mg/dL (16-201 mg/dL)
  - CK 299 U/L (0-165 U/L)
  - Inhibitor screen positive

Factor VIII 22% (50%-149%)
Anti-smooth muscle Antibody positive 1:2560 (<1:20)
Cholesterol 47 mg/dL (130-240 mg/dL)

BIOPSY:

A 4 mm punch biopsy shows leukocytoclastic vasculitis

Direct Immunofluorescence: IgA deposits in the vessel walls

DIAGNOSIS:

IgA Vasculitis

TREATMENT AND COURSE:

The patient's dose of prednisone was escalated to 80 mg daily. Over the following week the lesions formed slightly hemorrhagic bullae as anticipated, but stopped enlarging and began to fade. The bullae are healing and the patient shows daily improvement.

DISCUSSION:

IgA vasculitis is a small vessel vasculitis characterized by palpable purpura that may be accompanied by arthralgias, gastrointestinal signs and symptoms and glomerulonephritis. It has a tendency to persist longer than 2 weeks, to recur several times over a period of weeks or months, to show necrosis and to involve extracutaneous sites.

As IgA vasculitis can occur in both adults and children, the term HSP is controversial. Some authors regard HSP as any syndrome of leukocytoclastic vasculitis that is associated with arthritis or arthralgias, fever, abdominal pain, and renal disease with hematuria or proteinuria, regardless of or, in the absence of, direct immunofluorescence studies of lesional skin. Other authors regard the significant presence of IgA deposition in the affected vessels as important in the definition of HSP regardless of the presence or absence of extracutaneous findings. This discussion will use the more specific term of IgA vasculitis.

IgA vasculitis may be due to an underlying disease such as, lupus, cryoglobulinemia, multiple myeloma or IgA gammopathies, medications, previous upper respiratory infection with group A β-streptococcus, food sensitivity, pregnancy, familial Mediterranean fever, cancers (lymphoma, colon, bronchial, prostatic), insect bites, trauma, or the condition may be familial. These associations should be sought prior to a diagnosis of idiopathic IgA vasculitis.
When evaluating the patient with palpable purpura, it is important to note the presence or absence of inflammation, the size of the lesions, the pattern of hemorrhage, the presence of necrosis and

the margins of the lesions, smooth versus retiform. Each of these criteria will direct your differential and lead to a specific diagnosis. For example, the presence of inflammation as seen in this patient gives only 3 possible categories of disease, immune complex leukocytoclastic vasculitis, pauci-immune leukocytoclastic vasculitis and other including EM, PLEVA, chronic pigmented purpura and hypergammaglobinemic purpura of Waldenstrom. The morphologic characteristics noted above specifically help to elucidate a diagnosis of IgA vasculitis due its unique presentation. The distinctive lesions of IgA vasculitis consist of plaques of palpable purpura containing multifocal areas of hemorrhage or necrosis, usually arranged in a livedoid pattern with retiform margins. On direct immunofluorescence, Piette and Stone showed that these distinctive lesions have IgA deposits in the vessel wall as compared to typical palpable purpura without necrosis or retiform margins that display deposition of IgM, IgG, or C3 in vessel walls. Since IgA deposition is central to the diagnosis, it is important to biopsy for DIF. Other investigation may include a urinalysis, renal function and stool testing for occult blood.

Identifying IgA vasculitis is important regardless of one's definition of HSP, since studies suggest that vessel injury associated with IgA immune complexes is more likely than IgM- or IgG-immune complex-associated injury to result in a more long term course in the skin, more frequent cutaneous necrosis, a more beneficial effect from early systemic corticosteroid therapy, or a higher incidence of systemic extracutaneous disease.

Treatment of IgA vasculitis should be guided by the clinical findings. Identify and eliminate possible causes such as infection or drugs. An underlying gammopathy might require cytotoxic therapy. Corticosteroids are recommended in severe cases especially those with intestinal obstruction. Dapsone and colchicine may prove effective in treating the acute cutaneous disease or the arthralgias. In patients with renal involvement recognition and treatment of hypertension, preferably with an angiotensin-converting enzyme inhibitor, is the most effective measure known to influence the progression of idiopathic IgA nephropathy.

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Case #3

PRESENTED BY: *Jerry Feldman, M.D. and Meredith Stewart, M.D.*

HISTORY OF PRESENT ILLNESS:

This is a healthy 32-year-old woman who presented for evaluation of treatment options for multiple nevi on the left side of her face. These lesions were present since birth and have grown in size and number in proportion with her as she aged. In the recent past, the only change that she notes is darkening in color with sun exposure. There has been no change in the shape or size of any individual lesion or growth of new lesions in past several years. Approximately 5 years prior to presentation, she was evaluated at Northwestern University and diagnosed with nevus spilus. She had approximately 5 laser treatments with a Ruby laser over a two-year period. Immediately after each procedure, the patient noted lightening of the individual lesions. However, the lesions returned to the original color within several weeks after each treatment. She had no previous biopsies of any lesions on her face.

PAST MEDICAL HISTORY:

None

MEDICATIONS:

No known drug allergies

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory. No history of similar skin lesions. No history of melanoma or skin cancer.

SOCIAL HISTORY:

Non-contributory

Case #3 - Continued

PHYSICAL EXAMINATION:

There are approximately 200 light and medium-brown round and ovoid macules and flat papules 2-5 mm in size clustered in an area 6 x 8 cm on the left side of the face and anterior to the ear. Many of the lesions have a speckled slightly irregular appearance. There does not appear to be any background pigmentary changes around any of the pigmented lesions. There is a slight increase in vellus hair growth in the affected area. The rest of the skin exam reveals a 0.5 cm round medium brown macule at the angle of the jaw on the left face and multiple regular appearing brown nevi to the face, trunk and extremities.

LABORATORY EXAMINATION:

None indicated

BIOPSY:

3 mm punch biopsy from the left cheek revealed nests of normal appearing melanocytes at the dermoepid

DIAGNOSIS:

Agmintated Congenital Melanocytic Nevi

TREATMENT AND COURSE:

To be discussed

DISCUSSION:

Agminated melanocytic nevi are an uncommon clinical entity. Pigmented lesions that have been described in the literature as agminated include blue nevi, multiple lentigines, Spitz nevi, congenital melanocytic nevi, acquired melanocytic nevi, and lesions within a nevus spilus. Most reports of agmintated pigmented lesions in the literature correspond to Spitz or blue nevi. There are, however, multiple reports of agminated congenital melanocytic nevi which are often distributed in a mosaic pattern that may follow Blaschko's lines or dermatomes. Our patient was previously given the diagnosis of nevus spilus, which is characterized by the presence of a lightly pigmented lentiginous patch containing scattered, more darkly pigmented macules and papules and typically appears during late infancy or early childhood. The absence of clinically visible background pigmentation, and the presence of these lesions at birth, makes the diagnosis of agminated congenital melanocytic nevi more suitable for this patient.

Case #3 - Continued

The management and treatment of congenital melanocytic nevi (CMN) is a controversial topic

because of the lack of valid data concerning the incidence of malignant changes within small CMN. Various therapeutic approaches, such as surgical excision, dermabrasion, cryosurgery, electrosurgery, carbon dioxide laser therapy, have been used to treat CMN, but all of these methods produce postoperative scarring and alterations in pigmentation and skin texture. Laser therapy of pigmented lesions, particularly CMN, is a controversial topic. As with surgical excision, it is hypothesized that the destruction of nevomelanocytes by laser therapy should reduce the risk of malignant transformation by reducing the population of nevus cells. The potential malignant transformation with nonlethal laser exposure is not well studied. Unlike UV light, the effects of lasers on tissue are primarily thermal. Nevomelanocytes in the epidermis and dermis are destroyed by selective photothermolysis of melanosomes. However, preliminary in vitro studies have demonstrated that laser irradiation of human melanoma cell lines significantly increases DNA damage leading to an increase in p16 expression, a proposed candidate gene in melanoma. Additionally, stimulation of melanocyte proliferation and migration have been observed subsequent to the exposure of these cells in vitro to media derived from keratinocytes exposed to low-energy lasers. These findings may suggest that the effect of lasers on tissues is, perhaps, more than just thermal in nature and that long-term mutagenic risks may exist. Nevertheless, there are no reported cases of malignant transformation after laser use in pigmented lesions.

Many lasers have been used in the treatment of CMN. The carbon dioxide laser, which emits light at a wavelength of 10,600nm is absorbed by water. In general, continuous wave carbon dioxide laser ablation causes extensive scarring and is reserved for removal of epidermal lesions because the removal of deeper, dermal lesions is associated with unacceptable tissue scarring. Ultra-short high energy pulsed carbon dioxide lasers have a smaller zone of thermal damage and have been successfully used in the treatment of giant CMN in newborns. Pigment-specific lasers that have been well studied in the treatment of CMN and are the most widely used today. These include the Q-switched ruby laser (694nm), Q-switched Alexandrite laser (755nm), the normal mode Ruby laser, the normal mode Alexandrite laser, and the Q-switched Nd-YAG (1064nm). Q-switched ruby laser has only partial effectiveness even after multiple treatments. The normal mode ruby laser seems to be the most effective laser for the treatment of CMN due to the longer pulse, and thus enhanced penetration of the 694nm laser light. Additionally, comparative studies demonstrate an improved clinical response when lesions were treated with combined normal-mode plus Q-switched ruby laser than with the normal-mode ruby laser alone in Japanese patients. Combined use of ultra-short high energy pulsed carbon dioxide laser and Q-switched ruby or Nd:Yag laser has also shown to be effective in the treatment of CMN in infancy.

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Case #3 - Continued

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Case #4

UNKNOWN CASE

Case #5

PRESENTEDBY: *Jerry Feldman, M.D. and Jessie Cheung, M.D.*

HISTORY OF PRESENT ILLNESS:

This 23-year-old woman presented to our clinic with a history of lesions on the left arm since birth that have become more palpable with age, especially since puberty. The lesions become redder during the summer and are now painful to touch. She denied any previous trauma to the site, or melena.

PAST MEDICAL HISTORY:

None

MEDICATIONS:

None

ALLERGIES:

Penicillin

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

There are multiple discrete spongy dark blue nodules grouped on the left extensor arm. There is a solitary blue papule on the left flexor forearm. They are tender and non-pulsatile to palpation.

Case #5 - Continued

LABORATORY EXAMINATION:

None indicated

BIOPSY:

Dilated blood vessels are present throughout the dermis. The vessels are lined by one or two layers of uniformly cuboidal cells.

DIAGNOSIS:

Glomuvenous Malformation

TREATMENT AND COURSE:

The patient is awaiting an MRI of her arm. We are considering pulse-dye laser therapy or sclerotherapy after the extent of the glomuvenous malformation is delineated.

DISCUSSION:

The diagnosis and management of venous malformations has been hampered by confusion over terminology. Venous malformations (VMs) are composed of ectatic, thin-walled channels lined by flat endothelial cells and surrounded by a media that is irregularly deficient in smooth muscle cells. The channels permeate the epithelium, which contributes to the typical blue hue of cutaneomucosal venous lesions. Some VMs have variable numbers of glomus cells, which in the past, have been called multiple glomus tumors or glomangiomas. The term glomuvenous malformation (GVM) has been proposed to replace the older terms, since the lesions are not neoplastic.

Most VMs are sporadic, although there are a few families that exhibit autosomal dominant transmission of VM or GVM. Linkage analysis has revealed two different entities. Some hereditary cutaneomucosal VM (CMVM) are caused by a gain-of-function single amino acid change in the angiopoietin receptor TIE2/TEK, causing ligand-independent activation of an endothelial cell-specific receptor tyrosine kinase; localized to chromosome 9p21 (VMCM-1). Studies have shown that some hereditary GVMs are caused by several loss of function mutations in glomulin, localized to chromosome 1p21-22 (VMGLOM).

A recent study identified the significant clinical differences between inherited CMVM and GVM. CMVMs were of various hues of blue, while GVMs varied from pink in infants to deep blue or purple in children and adults. All GVMs involved skin and subcutis but rarely mucosa, and never extended deeply into muscle. CMVMs involved skin and oral mucosa, but also occurred in

Case #5 - Continued

skeletal muscle. GVMs were more likely to be localized to the extremities (78%), in contrast to CMVMs, which were in the cervicofacial area (50.3%) and extremities (37.1%). All GVMs were raised with a cobblestone-like appearance, except for the rare plaque-like variant; CMVMs were typically rounded. GVMs were slightly hyperkeratotic especially if located in an extremitiy, and not compressible by palpation, whereas CMVMs were not hyperkeratotic and were soft and easily emptied by external pressure. Pain from external pressure was the most common complaint for 55% of patients with GVMs, whereas 45% of patients with CMVMs noted pain after activity or with temperature change or with puberty and menstrual cycles, but not by compression. CMVMs were typically painful in the morning, which is probably due to stasis and expansion. Phleboliths are suggestive of VM (slow-flow with stasis and thrombosis). The appearance of new vascular lesions after trauma occurred in 17% of patients with familial GVM; this did not occur with CMVM. Sporadic GVM and inherited GVM were clinically similar in appearance and non-compressiblity, and with the involvement of skin and subcutis but rarely mucosa. All sporadic GVMs and CMVMs were diagnosed at birth, in contrast to inherited lesions; and the sporadic lesions were often single and extensive. Sporadic GVM was more common in the cervicofacial area (27%) compared with inherited GVM (8%).

It is important to distinguish between GVM and VM when planning therapy. Pain is usually aggravated by elastic compressive garments in a patient with GVM, while pain in a VM should be improved. Resection of a GVM may be easily accomplished since GVMs are typically located superficially, while VMs are often difficult to excise completely since they permeate surrounding tissue and may involve deep structures. Sclerotherapy with hypertonic saline or sodium tetradecyl sulfate has been performed successfully for GVMs. Ultrasound-guided sclerotherapy with polidocanol microfoam has been effective in treating CVMs. The NdYAG laser and CO_2 laser, and more recently, the pulsed dye laser, have also been used successfully for GVMs.

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Case #5 - Continued

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Case #6

PRESENTED BY: *Lissette Ortiz-Ferrer, M.D., Lisa Kates, M.D. and Alyssa Nash-Goelitz, M.D.*

HISTORY OF PRESENT ILLNESS:

This 14-year-old Hispanic boy presented to Cook County with a lesion on the left arm, lower chest, flank and abdomen since birth. He stated that over the past 3 years it had been increasing in size. He complained of occasional pruritus associated with the lesion. He denied any history of hepatitis or alcohol consumption. Otherwise, the patient was in good health and performing well in school.

PAST MEDICAL HISTORY:

None

MEDICATIONS:

None

ALLERGIES:

None

FAMILY HISTORY:

No family history of hepatitis

SOCIAL HISTORY:

No history of smoking, alcohol, or drug use.

PHYSICAL EXAMINATION:

The patient had erythematous pinpoint macules coalescing into patches on his left arm, lower left chest, flank, and abdomen that follow a dermatomal distribution. The lesions blanched with diascopy. There was no hemihypertrophy of the left arm. Also, the patient had mild bilateral gynecomastia.

Case #6 - Continued

LABORATORY EXAMINATION:

The following were normal or negative:
- Hepatitis A, B and C antibodies
- Liver function tests
- Testosterone and estrogen
- DHEAS

BIOPSY:

A biopsy from the left abdomen shows dilated thin walled blood vessels present within the upper dermis.

DIAGNOSIS:

Unilateral Nevoid Telangiectasia

TREATMENT AND COURSE:

Prior to presentation at Cook County Hospital, no treatments were attempted. A test spot was performed with the V-beam (pulsed dye laser) 595 nm with the following settings: 7 mm spot size, 3 ms pulse duration, and fluence of 7.0 J/cm^2. An immediate purpuric response was noted.

At the 4-week follow-up, there was complete resolution of the telangiectasias within the test area. At this time the abdomen was treated with a 10 mm spot size, 3 ms pulse duration, fluence of 7.5 J/cm^2 with an immediate purpuric response. For comparison, the chest and left arm were treated with a 10 mm spot-size, 6 ms pulse duration, and fluence of 7.5 J/cm^2 for a subpurpuric response. The patient was scheduled for follow-up after 4 weeks and possible treatment of any remaining telangiectasias.

DISCUSSION:

In the literature, unilateral nevoid telangiectasia is also known as “linear telangiectasia”, “unilateral spider nevi”, and “microtelangiectasia essential progressive unilateral.” Since the late 1970s, the terms unilateral nevoid telangiectasia and unilateral dermatomal superficial have been predominately used. It is classified as a malformation, an abnormal structure that results from an aberration in embryologic development. Specifically, it is a type of vascular malformation, a capillary or “low flow” type. Telangiectasia denotes a condition characterized by abnormal permanent dilatation of end vessels, mainly venules, but occasionally of capillaries and arterioles in the subpapillary plexus.

Case #6 - Continued

Unilateral nevoid telangiectasia may be acquired or congenital. The lesions are distributed unilaterally and consist of numerous threadlike telangiectases. It is characterized by a dermatomal distribution, most frequently involving the trigeminal and third and fourth cervical dermatomes. Histopathologically, dilated capillaries are seen in the upper parts of the dermis. Increased numbers of receptors for estrogen and progesterone have been reported in these dilated capillaries when compared to normal skin.

The congenital form of unilateral nevoid telangiectasia is more common in male patients, whereas the acquired form appears predominately in female patients. Our patient represents the twelfth patient of congenitally unilateral nevoid telangiectasia. The onset of acquired unilateral nevoid telangiectasia can be categorized into three groups: 1) at puberty, 2) during pregnancy, or 3) with alcoholic cirrhosis. There have been 2 recent cases describing young men with unilateral nevoid telangiectasia without evidence of cirrhosis, but with hepatitis C infection. The above 3 conditions all cause increased blood estrogen levels. Since circumstantial evidence indicates a major role for estrogen in the induction of telangiectasias and in the stimulation of angiomas, the unilateral dermatomal distribution of the superficial telangiectasia may suggest a congenitally fixed distribution of target end organs due to cutaneous morphogenesis patterns sensitive to estrogen. The onset of congenital unilateral nevoid telangiectasia could be explained by a postulated lower threshold to estrogen in the abnormal target end organs.

We believe that increased estrogen levels also played a role in our patient. He reported that the lesions seemed to spread with the onset of puberty. He also displayed evidence of gynecomastia which commonly occurs in this age group and is considered physiologic. The transient gynecomastia of adolescence may represent extraglandular estrogen production after adrenarche before pubertal testosterone secretion has begun.

Acquired lesions of unilateral nevoid telangiectasia tend to fade after pregnancy. It is reasonable to assume that following puberty, our patient's lesions would also tend to return to their pre-pubertal state. Our patient, however, was concerned the lesions were spreading and desired treatment. The pulsed dye laser (PDL) was the chosen therapeutic modality as it targets intravascular oxyhemoglobin to effect destruction of various congenital and acquired vascular lesions.

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Case #6 - Continued

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Case #7

PRESENTED BY: *Jerry Feldman, M.D., Tony Fu, M.D., Kastytis Jucas, M.D. and Alyssa Nash-Goelitz, M.D.*

HISTORY OF PRESENT ILLNESS:

This 79-year-old woman was referred to our clinic with a four-year history of hyperpigmented patches of her nasal bridge, cheeks, and orbital region. She stated that the lesions began as small irregular brown patches. She was subsequently treated with 4% hydroquinone (Alustra) for approximately one and a half years and 6% hydroquinone without imrovement. She denied any systemic symptoms such as arthritis, dark colored urine, dark cerumen, or other affected family members.

PAST MEDICAL HISTORY:

Hypertension

MEDICATIONS:

Hydrochlorothiazide/Valsartan

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

The patient exhibited slate gray macules and patches, which were especially prominent periorbitally and in the malar areas. The sclerae, conjunctivae, ears, and oral mucosa were normal.

Case #7 - Continued

LABORATORY EXAMINATION:

None indicated

BIOPSY:

A biopsy from the left lower canthus reveals, within the reticular dermis, multiple scattered, elongated, and curved collagen bundles that are stained yellow-brown.

DIAGNOSIS:

Exogenous Ochronosis

TREATMENT AND COURSE:

There has been no improvement with azelaic acid, 40% urea cream, or 2% kojic gel.

DISCUSSION:

Ochronosis was so named because histologically the pigment appears ochre colored (yellow), although clinically the pigment appears blue-black. Endogenous ochronosis, alkaptonuria, is an autosomal recessive disease caused by the absence of the enzyme homogentisic acid oxidase. This leads to the accumulation of homogentisic acid (HGA). It binds irreversibly to fibrillar collagen and eventually leads to skin pigmentation and/or joint arthropathy. Diagnosis may be made early in life, by the presence of dark urine or dark cerumen. More commonly, symptoms are not evident until the third or fourth decade when the diagnosis is made clinically or on urine testing with sodium hydroxide. Blue-black pigmentation occurs most commonly on the pinnae, nasal tip, cheeks, and sclerae and in regions of high sweat gland density such as the axillae. It may also appear in cartilage, tendons, tympanic membranes, cerumen, sclerae, nail beds, and axillary and genital skin.

Exogenous ochronosis was first reported in 1906. It commonly presents as asymptomatic blue-black macules on the malar areas, temples, inferior cheeks, and neck. This condition resembles endogenous ochronosis in the skin histologically, but does not exhibit any systemic complications or genitourinary abnormalities.

Histologic examination of exogenous ochronotic lesions reveals yellow-brown banana-shaped fibers in the papillary dermis. Homogenization and swelling of the collagen bundles is noted and a moderate histiocytic infiltrate may be present. Sarcoid-like granulomas with multinucleated giant cells engulfing ochronotic particles have been noted. Ochronotic fibers stain black with Fontana stain and blue-black with methylene blue stain.

Hydroquinones are by far the most common offending agents, but phenol, quinine injection, and resorcinol have also been implicated. Exogenous ochronosis has been reported mostly in South African black patients, where hydroquinone-induced exogenous ochronosis has been found in 28%-35% of the black population. Although it was originally believed that only high concentrations of hydroquinone were causal, there have been reports of ochronosis after use of 2% hydroquinone preparations. It has also been suggested that the percentage of hydroquinone quoted by a manufacturer may not necessarily represent the true concentration of hydroquinone in a product. It may be that it is not the high concentration of hydroquinone, but rather, extended use of this substance, which causes the disease.

The cause of exogenous ochronosis is unclear. Topical hydroquinones may inhibit homogentisic acid oxidase in the skin, resulting in the local accumulation of homogentisic acid that then polymerizes to form ochronotic pigment. Pigmented particles may be elastic or collagen fibers. Another hypothesis is that functional melanocytes may play an important role in the pathogenesis of ochronosis. A patient with vitiligo who was attempting to lighten normal, remaining skin on the face developed ochronosis in these areas. Interestingly, the vitiliginous areas remained white, supporting the role of functional melanocytes in the pathogenesis of ochronosis. Sun exposure may activate melanocytes and explain the distribution of ochronosis as well.

Treatment of exogenous ochronosis has been disappointing. Tretinoin gel, cryotherapy, and trichloroacetic acid have been tried without benefit. Most authors have suggested letting the lesions fade over time. Clinical improvement has been reported after treatment with dermabrasion and carbon dioxide laser, however results have not been uniform. Recently, Alster has reported successful treatment of ochronosis in two patients with the Q-switched alexandrite laser.

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Case #8

PRESENTED BY: *Jonith Breadon, M.D. and Samantha Golden, M.D.*

HISTORY OF PRESENT ILLNESS:

This 32-year-old African-American woman presented to the dermatology clinic in 2003 complaining of acne, excessive facial hair, darkening of her skin and razor bumps in her beard area from shaving. The patient reported normal menstrual cycles.

PAST MEDICAL HISTORY:

None

MEDICATIONS:

None

ALLERGIES:

None

FAMILY HISTORY:

Positive family history of diabetes mellitus, hypertension, and similar skin findings.

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

The patient had hyperpigmentation and hirsutism of the beard area as well as small red, inflamed, slightly keloidal papules on her cheeks and under her chin. She also had open comedones, closed comedones, and erythematous papules mostly on her cheeks and under her chin.

Case #8 - Continued

LABORATORY EXAMINATION:

The following was normal or negative:
Serum glucose

BIOPSY:

None performed

DIAGNOSIS:

Pseudofolliculitis Barbae

TREATMENT AND COURSE:

The patient's postinflammatory hyperpigmentation is being treated by a 3% hydroquinone solution. Benzoyl peroxide gel 5% and fluocinonide .05% gel were prescribed to treat the areas of pseudofolliculitis barbae. She had also tried to avoid shaving and tweezing, but her facial hair was cosmetically unacceptable to her. The patient started laser treatment for hair removal in her beard area with the 1064nm long pulse ND-YAG laser in May 2004. The following laser parameters were utilized: Treatment 1: fluence 30 J/cm2, pulse width 40ms; Treatments 2, 3, 4: fluence 35 J/cm2 and pulse width 35 ms.

DISCUSSION:

Pseudofolliculitis barbae (PFB), first described by Fox in 1908, is a foreign body inflammatory reaction surrounding in-grown hair that results from shaving, waxing, or plucking. Hair removal is the precipitating factor of PFB especially in patients with tightly curled course hair. This condition can be seen in all races and both genders, but is most common in black men with a prevalence of 45-83%. PFB occurs when strongly curved hairs emerging from the follicle are cut obliquely in the process of shaving, giving them sharp points. As the hairs grow, they curve back toward the epidermis and the sharp points penetrate the epidermis and dermis within a short distance from the follicle. The hair shaft becomes ensheathed with epithelial cells, becoming a pseudofollicle. As a result, a foreign body reaction provoked by the ingrown hair develops and is manifested by inflammatory papules and pustules, often accompanied by fibrotic scarring and hyperpigmentation.

Treatments for PFB should include elimination of ingrown hairs. Discontinuation of shaving is usually the first option for patients with PFB. Many men are unwilling or unable to grow a full beard, and this option is cosmetically appalling for women. A shaving tool that avoids a close shave is of paramount importance. Many women have opted for chemical depilatories like barium sulfide and calcium thioglycolate. These lyse the disulfide bonds of the hair and cause

Case #8 - Continued

feather-tipped ends, which are less likely to result in ingrown hairs. Adverse reactions to depilatories include irritation, and chemical burns. Eflornithine hydrochloride cream is a relatively new medication that irreversibly inhibits ornithine decarboxylase resulting in inhibition of hair growth. Other methods, however, need to be utilized to remove the hair initially. This cream is currently expensive, but is a good adjunct to other therapies. Medical therapy had previously not been curative for PFB, but lasers for hair removal, have now redefined the treatment.

With the advent of longer wavelengths, longer pulse durations, and more efficient cooling devices, the appropriate candidate for laser assisted hair removal is no longer the fair-skinned individual with dark terminal hairs, but also includes patients with darker skin types (V and VI). Laser light must pass through the pigmented epidermis to target the dermal hair follicle. The main challenge in treating pigmented skin is the presence of melanin in the epidermis competing as a chromophore for laser light, and the conversion of laser energy into heat, causing blistering, dyschromia and scarring. The absorption spectrum of melanin is 250-1200nm. The absorption of melanin decreases as the wavelength increases. Longer wavelengths allow for greater depth of penetration, resulting in less epidermal absorption. A longer pulse duration allows for more efficient cooling of the epidermis. Smaller structures lose heat more quickly than larger structures, so the longer pulse duration allows the heat in the epidermal melanin to dissipate more quickly than in the dermal hair follicles, thereby protecting the epidermis from thermal damage. Aggressive adjunct cooling during treatment is especially important in minimizing epidermal thermal damage.

For patients with darker skin, only lasers that combine the characteristics previously mentioned can safely be used for hair removal. The two lasers that have been successfully used are the 810nm diode and the 1064nm Nd:YAG. The 1064nm Nd:YAG laser is safer because of the longer wavelength, but consequently is less effective than the diode. The diode laser utilizes pulse durations of 100 milliseconds or longer. This laser is best suited for skin phototypes I-V. To safely treat phototype VI, very long pulse durations (400 milliseconds and longer) as well as aggressive adjunctive skin cooling should be used. The 1064nm Nd:YAG laser can be safely used with shorter pulse durations because the longer wavelength penetrates deeper into the dermis. The pulse durations of the 1064nm Nd:YAG laser range from 3 milliseconds to greater than 100 milliseconds. Multiple studies have supported the efficacy and safety of the 1064 nm long pulsed, Nd:YAG laser for the treatment of pseudofolliculitis barbae in skin types V and VI.

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Case #8 - Continued

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Case #9

PRESENTED BY: *Warren W. Piette, M.D. and Anne Snider, M.D.*

HISTORY OF PRESENT ILLNESS:

This 43-year-old Hispanic female with a seven-year history of myelodysplastic syndrome presented with non-tender chest nodules for 6 months. The patient also noted a nodule present for 4 years which she said had been diagnosed as an umbilical hernia.

PAST MEDICAL HISTORY:

Myelodysplastic syndrome diagnosed in 1997 with progression to acute myelogenous leukemia in 2004 status post chemotherapy.

MEDICATIONS:

Acyclovir
MS Contin
Tylenol
Multivitamin

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

On the chest there are red-brown, non-tender, moderately firm subcutaneous nodules. There are several ecchymoses on the breasts and shoulders. A very firm, non-tender skin-colored tumor is present periumbilically.

Case #9 - Continued

LABORATORY EXAMINATION:

The following were abnormal or positive:

Blood urea nitrogen=68 mg/dL (8.0-20.0 mg/dL)
Creatinine=2.1 mg/dL (0.6-1.4 mg/dL)
Calcium=6.5 mg/dL (8.5-10.5 mg/dL)
White blood cell count=107.2 k/uL (3.7-10.5 k/uL); 18% monocytes (2-12%), 7% neutrophils (40-82%), 9% lymphocytes (12-44%), 65 % blasts
Red blood cell count=3.10 mil/uL (3.76-5.06 mil/uL)
Hemoglobin=9.9 g/dL (11.5-15.4 g/dL)
Hematocrit=27.2% (34.3-45.2%)
Platelets=77 k/uL (167-400 k/uL)

BIOPSY:

A. A 4 mm punch biopsy of the chest shows a nodular and diffuse infiltrate of atypical mononuclear cells. Some of the cells contain mitotic figures. Strands of cells are lined up in an "indian file" formation.
B. A 5 mm punch biopsy of the periumbilical nodule shows a less dense collection of atypical mononuclear cells in the deep dermis.

DIAGNOSIS:

Leukemia cutis in the setting of myelodysplastic syndrome with excess blasts transforming to acute myelogenous leukemia.

TREATMENT AND COURSE:

The patient is being managed by hematology/oncology and is awaiting further chemotherapy and possible allogeneic bone marrow transplantation.

DISCUSSION:

Leukemia cutis is an uncommon cutaneous eruption which can be difficult to diagnose both clinically and histologically. Clinical presentation is variable ranging from firm papules, plaques or nodules (most commonly) to ulcers, macules, ecchymoses, palpable purpura and bullae. The papules, nodules, and plaques are typically skin-colored, pink, or red-brown to violaceous and can become purpuric with co-existing thrombocytopenia. Leukemic infiltration of the fat can simulate erythema nodosum. Leukemia cutis lesions primarily affect the face and extremities in acute and chronic lymphocytic leukemia, the trunk in granulocytic leukemia and the skin or mucous membranes in monocytic leukemia. Infiltrates on the face can

Case #9 - Continued

result in leonine facies. Leukemia cutis can localize to sites of previous trauma, burns, herpes simplex and zoster, and recent surgery. Gingival hypertrophy due to leukemic infiltration has only been seen in acute myeloid and monocytic leukemias. Chloromas can occur in acute

granulocytic leukemias and chronic granulocytic leukemia shortly before blast transformation. This tumor results from infiltration of myeloblasts into the skin. It gets its name from the green color of freshly cut specimens, which is due to the high cellular concentration of myeloperoxidase. The more general name has been granulocytic sarcoma rather than chloroma because many of the specimens are not sectioned and thus do not appear green. The name granulocytic sarcoma has recently been changed to myeloid sarcoma in the WHO classification.

Acute leukemia subtypes in which leukemia cutis has been reported include acute granulocytic leukemias, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, acute lymphoblastic leukemia and the leukemic phase of non-Hodgkin's lymphoma. Chronic leukemia subtypes in which leukemia cutis has been reported include chronic granulocytic leukemia, chronic lymphocytic leukemia, adult T-cell leukemia/lymphoma, T-cell prolymphocytic leukemia, hairy cell leukemia and chronic myelomonocytic leukemia. Leukemia cutis may also be seen with myelodysplastic syndromes and polycythemia vera. The incidence of leukemia cutis varies with the type of leukemia, ranging from 1% - 50%. The incidence is highest in the monocytic leukemias. Early cutaneous involvement occurs more frequently in acute myelomonocytic and monocytic leukemias. In chronic leukemias, skin involvement has been associated with transformation into the blastic phase and may suggest disease progression. When occurring with myelodysplastic syndrome, leukemia cutis often heralds malignant transformation to acute myeloid leukemia. In this situation, prompt diagnosis may identify a group of high-risk patients with myelodysplastic syndrome that should be treated more aggressively. This case seems unusual because of the 4-year presence of a very firm nodule which is leukemia cutis by biopsy.

The majority of the time leukemia cutis presents in the setting of established leukemia or the patient may present concomitantly with systemic leukemia. Skin involvement usually indicates advanced leukemia and may be a marker of rapid disease progression as leukemia cutis is strongly associated with the presence of extramedullary disease at other sites. On occasion, leukemia cutis may manifest before systemic disease. This is referred to as aleukemic leukemia cutis. The prognosis of leukemia cutis patients is usually quite poor. In a study by Longacre et al, 82% of patients with acute leukemia died within 1-24 months (mean, 5.5 months) of the diagnosis of leukemia cutis; this is comparable to the 8-month mean survival reported by Meis et al in their series of cases of granulocytic sarcoma. The treatment of leukemia cutis starts with treating the underlying systemic leukemia. This is most often achieved with chemotherapy alone or with radiation therapy.

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Case #9 - Continued

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Case #10

PRESENTED BY: *Warren W. Piette, M.D. and Shirley Chi, M.D.*

HISTORY OF PRESENT ILLNESS:

This 22-year-old Hispanic man presented with slowly growing lesions of 9 months duration on his arms. He also reported a 15-pound weight loss over the previous 3 months. He denied any trauma, cough, dyspnea, fevers, or chills.

PAST MEDICAL HISTORY:

None

MEDICATIONS:

None

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Immigrated from Mexico 2 years ago. He works in an assembly line at an aluminum manufacturing plant in Chicago. He denies tobacco and alcohol use.

PHYSICAL EXAMINATION:

A 10 x 6 cm foul-smelling, yellow, crusted and vegetative plaque was present on the left lateral arm. A similar sharply-demarcated, crusted plaque with minimal surrounding erythema was present on the right medial arm. There were palpable lymph nodes in bilateral axillae.

Case #10 - Continued

LABORATORY EXAMINATION:

The following were normal or negative:
- Basic metabolic panel
- Complete blood count
- Liver function tests
- HIV Ab
- PPD
- Tissue culture for acid fast bacilli

The following were abnormal or positive:
- Tissue fungal culture: positive for broad based budding yeast consistent with blastomycosis
- Tissue bacterial culture: 4+ staphylococcus aureus

Chest radiograph:
Left heart border is silhouetted by infiltrate suggesting possible pneumonia in the lingula. No pleural effusion. No evidence of pulmonary edema. No cardiomegaly.

BIOPSY:

Skin:
Left arm, 4 mm punch: Pseudoepitheliomatous hyperplasia is present with small abscesses. Lymphocytes and plasma cells are present throughout the dermis. Occasional yeast forms can be visualized in the H&E sections.

DIAGNOSIS:

Blastomycosis

TREATMENT AND COURSE:

Treatment was initiated with oral itraconazole 200 mg daily with gradual improvement of the lesions. The patient continues to be seen by the division of infectious disease on an outpatient basis.

DISCUSSION:

Blastomycosis is caused by a dimorphic fungus, *Blastomyces dermatitidis*, that exists in nature in a mycelial phase and converts to a yeast phase at body temperature. The soil is the most important source of infection and the respiratory tract is typically the first site of infection. Endemic areas include the southeastern or south central states bordering Mississippi or Ohio River basins, the Midwestern states and Canadian provinces bordering the Great Lakes, and a

small area in New York and Canada along the St. Lawrence River. While all ages and genders can be affected, adult men are most like to develop systemic infection, and children are more likely to develop acute pulmonary blastomycosis rather than chronic cutaneous disease. In contrast to histoplasmosis and coccidioidomycosis, blastomycosis is not a common infection in patients infected with HIV.

The respiratory system is typically the first site of infection, via inhalation of organisms. Pulmonary blastomycosis may be asymptomatic or produce mild to moderately severe acute pulmonary signs such as fever, chest pain, cough, and hemoptysis. Secondary cutaneous dissemination is a common occurrence, as the skin is the most common extra-pulmonary site of spread followed by bone, prostate, and central nervous system. Cutaneous lesions may be the first sign of disease, and may even be seen in the absence of overt pulmonary disease, as was the case in our patient. Primary cutaneous inoculation is very rare and occurs almost exclusively as a laboratory or autopsy room infection.

Skin lesions in blastomycosis are either verrucous or ulcerative. The verrucous, or fungating, form is raised and has a sharp but irregular border, the base of which commonly contains exudate. Biopsy of these lesions shows papillomatosis and downward proliferation of the epidermis with intraepidermal abscesses. Closer histological examination demonstrates round yeast forms with characteristic broad-base budding and thick double-contoured walls. Detection of fungus by cultures or histological exam confirms the diagnosis of infection.

Current recommendations for non-life threatening, non-CNS blastomycosis in a compliant patient include treatment with itraconazole, at an initial dosage of 200 mg daily, for at least 6 months. Because of less toxicity and despite its higher cost, itraconazole has replaced ketoconazole as first-line therapy. However, for severe life-threatening CNS disease, or disease in a significantly immunosuppressed patient (AIDS, transplant) amphotericin B remains the drug of choice.

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Case #11

PRESENTED BY: *Warren W. Piette, M.D. and Gina Dillig, M.D.*

HISTORY OF PRESENT ILLNESS:

This 39-year-old HIV positive man presents with slowly growing lesions of 8-months duration on the face and legs. He reported pain, pruritus and occasional purulent discharge. He also notes fevers and weight loss.

PAST MEDICAL HISTORY:

AIDS (HIV+ for fifteen years)
Hepatitis C infection

MEDICATIONS:

Dapsone
Azithromycin
No HARRT

ALLERGIES:

Sulfa drugs
Tetracycline
Penicillin

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Smoker. Occasional alcohol. History of intravenous drug use.

PHYSICAL EXAMINATION:

Three round verrucous plaques with overlying yellow crust on the right cheek, right upper lip and right chin measuring 4 cm, 2 cm and 2 cm respectively. There is no palpable cervical

lymphadenopathy. Larger crusted nodules approximately 1- 1.5 cm in size were present pretibially.

LABORATORY EXAMINATION:

LESIONAL KOH SCRAPING (performed in clinic):
Specimen stained with toluidine blue, basic fuschin in 30% ethyl alcohol demonstrated multiple yeast spores with thick capsular walls and broad-based budding yeast forms

The following were negative or normal:
General Chemistry
Aspartate aminotransferase
Hemoglobin/ hematocrit
Platelet count
Blood culture
RPR
Chest X-ray
CT brain
CSF analysis and culture

The following were abnormal or positive:
White blood count 3.8 k/μL (3.7-10.5 k/μL)
CD4 7
Alanine aminotransferase 39 U/L (5-35 U/L)
Lactate dehydrogenase 214 U/L (85-210 U/L)
Tissue fungal culture 3+ *Cryptococcus neoformans*
Tissue bacterial culture 4+ *Methicillin Resistant Staphlococcus Aureus*
Serum latex cryptococcal Ag positive titer 1:4

BIOPSY:

A 4 mm punch biopsy shows suppurative and granulomatous inflammation with fungal organisms compatible with *Cryptococcus neoformans*.

DIAGNOSIS:

Secondary Cutaneous Cryptococcosis

TREATMENT AND COURSE:

The patient was placed on intravenous amphotericin B 60 mg daily and fluconazole 400 mg daily. The amphotericin was discontinued after 2 weeks and the fluconazole was continued. Oral

linezolid 600 mg twice daily and clindamycin 300 mg three times daily were started for the co-existent MRSA infection. Weekly azithromycin and atorvaquinone were continued for AIDS prophylaxis. The lesions are slowly clearing and the patient was started on antiretroviral therapy.

DISCUSSION:

Cryptococcosis is an opportunistic mycotic infection caused by *Cryptococcus Neoformans.* The organism is a ubiquitous yeast found in the soil, dust, human skin and pigeon droppings. *Cryptococcus* is usually inhaled resulting in a primary pulmonary infection in 90% of patients. In the remaining 10%, the organisms hematogenously disseminates to the central nervous system, bone and skin. Meningitis is the most common manifestation as the organism has a special affinity for the CNS.

Cryptococcosis is the most common life-threatening fungal infection in patients with AIDS. Between 6% and 13% of patients with AIDS are infected by *Cryptococcus* and of those, 50% will develop disseminated disease and 6% will have skin lesions. Secondary cutaneous cryptococcosis refers to patients with disseminated disease and skin lesions. Rarely, inoculation of the skin can result in primary cutaneous cryptococcosis, however the diagnosis is made only after a negative systematic evaluation.

Skin infection with cryptococcus occurs most frequently in the head and neck. A variety of morphologic lesions have been reported, including subcutaneous swellings, blisters, tumor-like masses, palpable purpura, pyoderma-gangrenosum-like ulcers, granulomas, papules, nodules, pustules, plaques, molluscum-like lesions, Kaposi's sarcoma-like lesions, draining sinuses and abscesses. Suspicious lesions should be biopsied and sent for tissue culture. Clinicians need to be aware of the varied morphologic characteristics, since cutaneous lesions can present in advance of other signs of systemic infection.

Histologic findings in cryptococcosis can occur as two types of reaction patterns. The first type is gelatinous, characterized by minimal tissue reaction with masses of organisms causing mucoid degeneration of invaded tissue. The second type is granulomatous, associated with few yeast cells and a pronounced tissue reaction, with histiocytes, giant cells, lymphocytes and areas of necrosis.

The organism is easily demonstrated in histologic sections with PAS stain. *Cryptococcus neoformans* is an oval or rounded, thick-walled spherule measuring 5 to 20μm in diameter. The polysaccharide capsule surrounding the organism can be visualized with methylene blue, Alcian blue, or mucicarmine. India ink preparation of the CSF or lesional exudate will also demonstrate the capsule. Cryptococcosis is also known as European blastomycosis, both for its clinical presentation and for the presence of broad-based budding yeast forms in tissue.

Due to the co-existence of cryptococcemia and skin lesions, this patient was diagnosed with secondary cutaneous cryptococcosis. Immunocompromised patients, especially those with AIDS should be treated in the same fashion as patients with CNS disease. The protocol follows an induction, consolidation and suppression strategy. The induction phase consists of amphoteric in B (0.7-1 mg/kg daily) plus flucytosine (100 mg/kg daily) for 2 weeks followed by consolidation with fluconazole (400 mg daily) for 10 weeks, then suppression with fluconazole (200 mg daily)

for life. Itraconazole (200-400 mg daily) is an acceptable alternative for individuals unable to tolerate fluconazole.

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Case #12

PRESENTED BY: *Sidney Barsky, M.D. and Alyssa Nash-Goelitz, M.D.*

HISTORY OF PRESENT ILLNESS:

This 7-year-old female was evaluated by the consult service in May 2004 for a three-day history of hyperpigmented linear streaks located on her scalp, trunk, and extremities. She was diagnosed with a dysgerminoma in March 2004 and underwent a resection of the tumor. She was currently receiving her third round of chemotherapy. Her mother reported similar lesions approximately 1 month ago during chemotherapy treatment. The patient denied any associated itching.

PAST MEDICAL HISTORY:

Dysgerminoma

MEDICATIONS:

Etopiside
Cysplatin
Bleomycin

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

There were numerous brown linear streaks on the scalp, trunk, and extremities. No erythema or inflammatory lesions was noted.

Case #12 - Continued

LABORATORY EXAMINATION:

The following were abnormal or positive:

White blood cell count 3.1 k/*u*L (4.5-13.5 k/*u*L)
Hemoglobin 10.8 g/dL (11.5-15.5 g/dL)
Hematocrit 31.4% (35%-45%)

The following were normal or negative:

General Chemistry
Liver function tests

BIOPSY:

None performed

DIAGNOSIS:

Bleomycin-Induced Flagellate Streaks

TREATMENT AND COURSE:

The flagellate streaks continue to diminish after discontinuation of chemotherapy.

DISCUSSION:

Bleomycin is an antibiotic with antineoplastic properties. It was first isolated from *Streptomyces verticillus* and inhibits the incorporation of thymidine into DNA. It is widely used in the treatment of such tumors such as squamous cell carcinoma and malignant lymphoma. Following its administration, bleomycin is inactivated in most tissues by a hydrolase. The skin and lungs both lack this enzyme and therefore high concentrations of bleomycin are found in these organs. This may explain why the skin and lungs are frequent sites of toxic reactions. In addition to the pulmonary changes of pneumonitis and pulmonary fibrosis, bleomycin-induced cutaneous changes include sclerosis, digital gangrene, onycholysis, radiation enhancement or recall, neutrophilic eccrine hidradenitis, and flagellate hyperpigmentation.

The overall incidence of hyperpigmentation in patients receiving bleomycin is approximately 30%. The flagellate streaks occur in 8%-20% of cases, generally occurring after a cumulative dose of between 90 mg and 285 mg. However, there have been reported cases of flagellate hyperpigmentation with doses as low as 15 mg parentally or 30 mg intrapleurally. The time lapse between administration of the drug and onset of the hyperpigmentation ranges from 1 day to 9 weeks. The lesions appear as linear bands or streaks in a flagellate fashion, most commonly seen over the back and chest. The hyperpigmentation usually occurs de novo, but less commonly

follows linear erythematous papules and plaques, or urticarial-like lesions. It may be associated with intense pruritus. Early histological changes include superficial and deep perivascular mixed cell infiltrates compatible with a hypersensitivity reaction. Pathological findings of flagellate pigment demonstrate hyperpigmentation of the basal cell layer and active melanogenesis.

The exact mechanism by which bleomycin leads to these pigment changes is unknown. It is thought by some to represent post-inflammatory changes. It is speculated that the linear pigmentation may be caused by scratching. This may induce subclinical vasodilation by a dermatographic mechanism resulting in an excessive local accumulation of bleomycin. However, as in our patient, the flagellate hyperpigmentation may occur in the absence of pruritus. Also, the reaction cannot be reproduced reliably, even when the patient is still receiving the drug.

The pigmentary changes associated with bleomycin have been reported to disappear on discontinuance of the drug. A patient with "bleomycin streaks" reported in the literature still had "streaks" 4 months after discontinuing bleomycin, although the intensity had diminished.

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Case #13

PRESENTED BY: *Sidney Barsky, M.D. and Anne Snider, M.D.*

HISTORY OF PRESENT ILLNESS:

This 54-year-old African-American male with high grade, mucoepidermoid carcinoma of the neck was admitted to the hospital for chemotherapy. He received 5 days of 5-fluoruracil 500 mg/m^2. Within 4-7 days of starting his chemotherapy, the inpatient team noticed darkening of the veins of his right arm, the arm in which the 5-fluorouracil was being infused.

PAST MEDICAL HISTORY:

Mucoepidermoid carcinoma of the neck, high grade
Type II Diabetes Mellitus
Hypertension

MEDICATIONS:

5-fluoruracil 500 $mg/m^2/d$
Nifedipine
Benadryl
Insulin
MS Contin

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Alcohol abuse
Smoker

Case #13 - Continued

PHYSICAL EXAMINATION:

There is a hyperpigmented, serpentine pattern following the venous network of the right arm and chest. The veins underlying the pigmented streaks are not tender, thrombosed or sclerosed and are still patent. In addition, there are purpuric patches on the arms. The nails, mucous membranes, palms, and soles show no abnormalities.

LABORATORY EXAMINATION:

The following were negative or normal:

PT=12.5 secs (11.4-13.8)
INR=0.99
PTT =24.7 secs (24.6-36.2)
Complete blood count
Comprehensive metabolic panel

BIOPSY:

None performed

DIAGNOSIS:

Serpentine Supravenous Fluorouracil Hyperpigmentation

TREATMENT AND COURSE:

The patient was continued on his course of chemotherapy.

DISCUSSION:

5-fluorouracil (5-FU) is an antimetabolite used systemically in the treatment of carcinomas as well as topically for premalignant skin conditions. Cutaneous reactions to systemic 5-FU are uncommon and seem to be dependent on dose and schedule. Various cutaneous findings, such as exacerbation of seborrheic dermatitis, a plaque-like eruption in a butterfly distribution resembling lupus erythematosus, inflammation of actinic keratoses, maculo-papular eruptions of the palms and forehead, and palmar-plantar erythrodysesthesia (PPE) have been reported. The most common pattern of cutaneous reactions to 5-FU is photosensitivity. This is manifested by erythema and/or hyperpigmentation. Hyperpigmentation has been observed involving irradiation portal sites, the skin overlying veins used for infusions, and the dorsal aspects of the hands, palms, soles, oral mucosa, nails and trunk. Less commonly reported cutaneous manifestations of

Case #13 - Continued

5-FU include palmar keratodermas and folliculitis of the forehead.

Hyperpigmentation of the epidermis overlying veins used for 5-FU infusions occurs in 2%-5% of patients treated with intravenous 5-FU. Because of the serpiginous appearance of the hyperpigmentation, the term "serpentine supravenous fluorouracil hyperpigmentation" is suggested. The mechanism of action is unknown, however it has been postulated that 5-FU causes a loss of endothelial cell integrity which allows the drug to leach from the vessels to the overlying melanocytes and result in hyperpigmentation by possibly altering the melanosome packaging within the keratinocytes. Biopsies of the hyperpigmented streaks has revealed diffuse basilar hyperpigmentation, prominent basilar dendritic melanocytes, rare necrotic keratinocytes, and a superficial perivascular lymphocytic infiltrate.

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Case #14

PRESENTED BY: *Warren W. Piette, M.D. and Shirley Chi, M.D.*

HISTORY OF PRESENT ILLNESS:

This 40-year-old African-American woman presented with a four-month history of a rash on her chest and face, which was noticed by her primary physician during work-up for new onset congestive heart failure. Examination of the rash during our consultation led to further questioning. The patient acknowledged having experienced muscle weakness and fatigue for the past several months, making it difficult for her to perform daily tasks such as brushing her hair.

PAST MEDICAL HISTORY:

Obesity
Asthma

MEDICATIONS:

Albuterol

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

The patient is morbidly obese, in no apparent distress. Patches of hyperpigmentation, hypopigmentation with telangiectasias are present on the upper chest, along with scattered crusted hyperpigmented papules and areas of atrophy. Examination of the face reveals erythematous patches on both cheeks, and there are 3-4 mm erythematous papules on both upper eyelids.

Nailfolds show telangiectasias.

LABORATORY EXAMINATION:

The following were abnormal or positive:

Creatinine kinase	756 U/L	(0-125 U/L)
Lactate dehydrogenase	251	(0-200)

The following were normal or negative:

Basic metabolic panel
Complete blood count
Liver function tests
Antinuclear antibodies
Urinanalysis
Carcinoembryonic antigen
CA 125
CA 19-9

Chest radiograph:
1. Cardiomegaly
2. Increased interstitial markings within both lung bases, nonspecific.

Two-dimensional echocardiograph:
1. Mild left atrial enlargement. Moderate concentric left ventricular hypertrophy.
2. Vigorous left ventricular systolic function. No regional wall motion abnormalities. All sections visualized.
3. Normal function of both left-sided valves.
4. No 2D evidence of right heart overload; no tricuspid regurgitation seen.
5. Probable left ventricular relaxation abnormality.
6. Very small pericardial effusion without hemodynamic effects.

Electrocardiogram:
No conduction abnormalities

BIOPSY:

Skin:
Chest, 4 mm punch: There is an interface dermatitis, vacuolar type, and a superficial perivascular lymphocytic infiltrate. Few melanophages are present in the upper dermis.

Muscle:
Left deltoid: Perivascular and interfascicular inflammatory infiltrates with adjoining groups of muscle fiber degeneration.

Case #14 - Continued

DIAGNOSIS:

Dermatomyositis

TREATMENT AND COURSE:

Oral prednisone 60 mg daily was initiated and patient noticed marked improvement of both skin and systemic symptoms within 2 weeks of starting treatment. She is concurrently taking calcium carbonate, 500 mg three times daily, and vitamin D, 800 units daily. A mammogram was performed which was read as normal, and the patient has also been seen by gynecology and internal medicine for cancer screening. She continues to follow-up with rheumatology as well as dermatology.

DISCUSSION:

Dermatomyositis (DM) is an idiopathic inflammatory condition that usually presents with proximal muscle weakness and characteristic skin findings including pink/violaceous papules over the knuckles (Gottron's papules), violaceous eyelid erythema (heliotrope rash), periungual telangiectasias, and a photoexacerbated eruption. Muscle weakness is generally symmetric, most frequently involving the shoulder girdle and sometimes the pelvic region. Since the recognition of subsets of dermatomyositis patients that either have no clinical evidence of proximal muscle weakness and no serum muscle abnormalities for 6 months or longer (amyopathic DM) and patients with DM-specific skin disease and no clinical evidence of muscle disease with subclinical signs of myositis on laboratory evaluation (hypomyopathic DM), a more inclusive disease group has been suggested for what had historically been referred to as the idiopathic inflammatory myopathies: *idiopathic inflammatory dermatomyopathies*.

Adult-onset DM has a significant association with occult malignancy. Evaluation for malignancy as directed by age- and sex-directed screenings, history and physical examination, laboratory evaluation and imaging studies is warranted. In women, screening for ovarian cancer is also indicated. Oral or intravenous pulse corticosteroids remain the treatment of choice for suppressing all manifestations of newly diagnosed adult- and juvenile-onset DM patients. Methotrexate, cyclosporine, and high-dose intravenous immunoglobulin (IVIG) have traditionally been used as steroid-sparing agents. Mycophenolate mofetil has also been reported to be of similar benefit. For cutaneous lesions, treatments include broad spectrum sunblocks, topical corticosteroids, antimalarials, and methotrexate. Dapsone, mycophenylate mofetil, and thalidomide have also been suggested anecdotally to be of value for cutaneous DM inflammation.

Our patient was originally admitted to the hospital with new-onset congestive heart failure, which deserves further comment in light of knowledge that cardiac disease can be one of the noncutaneous manifestations of dermatomyositis. Congestive heart failure has been observed in patients with dermatomyositis/polymyositis (DM/PM), as has conduction abnormalities, arrhythmias, myocarditis, pericardial tamponade, pericardial effusions, and pericarditis. Earlier reports suggest that cardiac involvement in the form of congestive heart failure occurs in DM/PM but that it is infrequent. However, a study done by Haupt and Hutchins comparing clinical and

autopsy results of affected patients showed 7 out of 16 patients (44%) with dermatomyositis, dermatomyositis with malignancy, childhood dermatomyositis, and DM/PM overlap syndrome to have both clinical and pathological evidence of cardiac involvement manifesting as congestive heart failure. Evidence of myocardial involvement included active myocarditis, focal fibrosis, vasculitis, intimal proliferation, and medial sclerosis of vessels. These findings suggest that cardiac involvement in polymyositis and dermatomyositis is not uncommon. While the relationship of myocardial involvement to dermatomyositis cannot be ascertained by the non-invasive cardiac imaging studies in this case, it is a worthwhile consideration that underscores the importance of monitoring patients for symptoms of cardiac disease by history and examination.

TAKE-HOME MESSAGE:

Cardiac disease has been known to occur in dermatomyositis and should be considered in patients with previous or new diagnoses of myocardial conditions in the setting of dermatomyositis.

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Case #15

PRESENTED BY: *Jerry Feldman, M.D. and Anne Snider, M.D.*

HISTORY OF PRESENT ILLNESS:

This 37-year-old African-American female with hyperthyroidism secondary to Graves' disease presented with nodules on her great toes. Similar growths had been excised at an outside hospital one year prior but the nodules quickly reformed. On presentation, the patient was also noted to have significant exophthalmos as well as bulbous fingers and toes with clubbing.

PAST MEDICAL HISTORY:

Hyperthyroidism secondary to Graves' disease diagnosed in 1998 for which she received radioactive iodine in 2003.

MEDICATIONS:

Propylthiouracil (PTU)

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

There are well-demarcated, fleshy, mammillated nodules on the great toes. The patient also exhibits significant exophthalmos and bulbous fingers and toes with clubbing.

Case #15 - Continued

LABORATORY EXAMINATION:

The following were abnormal or positive:
T4=12.5 (0.60-1.70)
TSH=<0.03 (0.40-6.00)
Microsomal antibody screen positive

The following were normal or negative:
Thyroglobulin antibody screen

BIOPSY:

A 4 mm punch biopsy of the right great toe shows pooling of mucin throughout the dermis. A colloidal iron stain highlights dermal mucin.

Radiography:
Plain films of the hands show diffuse clubbing bilaterally. The tufts of the distal phalanges of all the fingers demonstrate a periosteal proliferation resulting in slight enlargement of the tufts, which demonstrate a lacy and bubbly pattern. These findings are pathognomonic for thyroid acropachy.

DIAGNOSIS:

Triad of exophthalmos, thyroid dermopathy of the great toes, and acropachy in a patient with Graves' disease

TREATMENT AND COURSE:

The patient's hyperthyroidism is being managed by endocrinology. Her T4 is now within normal limits and she is no longer taking PTU. She has received 6 injections of Kenalog 10 mg/cc into the nodules on her great toes which has resulted in softening of the lesions. Excision of the excess skin following the Kenalog injections is planned.

DISCUSSION:

Graves' disease, an autoimmune disease of the thyroid gland that follows the production of IgG autoantibodies directed primarily against the thyrotropin (TSH) receptor, is the most common cause of hyperthyroidism. The annual incidence of Graves' disease is approximately 80 per 100,000 women. Exophthalmos is found clinically in up to 30% of Graves' disease patients and is usually the first extrathyroidal manifestation of hyperthyroidism. Dermopathy occurs in 4% of patients with Graves' disease and in 15% of patients with Graves' related ophthalmic disease. Thyroid dermopathy is traditionally termed pretibial myxedema because of its propensity for the

Case #15 - Continued

anterior shins. However, as our case demonstrates, thyroid dermopathy is the preferable term because lesions may be found nearly anywhere. Dermopathy has also been seen in euthyroid states and does not appear to be related to levels of thyroid hormone. It may occur up to 14 years after the development of ophthalmopathy. The incidence of acropachy is 0.8%-1.0% and may be manifested up to 25 years after the onset of thyroid disease. The triad of ophthalmopathy, dermopathy, and acropachy tends to appear chronologically in the course of the Graves' disease in less than 1% of patients.

The pathogenesis of thyroid dermopathy is unknown. Histology shows deposition of mucin (glycosaminoglycans (GAG) and hyaluronic acid (HA)). The most recent studies suggest fibroblast-stimulating factor and insulin-like growth factor may be responsible for the increased localized overproduction of GAG and HA. Trauma may play a role, which might explain the propensity for lesions to occur on the anterior shins and in our case, the great toes. It has been shown that thyrotropin receptor antibody binding sites exist on pretibial fibroblasts. The receptors when stimulated induce large amounts of HA production. The receptor sites have also been demonstrated on orbital fibroblasts. In addition it is thought that T cells may induce HA production by stimulating a cytokine response after reacting with thyrotropin receptors. Thyrotropin receptors may also have germline mutations, which may explain the rare nature of the thyroid triad, as in our patient.

Treatment of the dermopathy is usually only of cosmetic concern, but occasionally severe disease may entrap the peroneal nerve or make shoes difficult to wear. Thyroid dermopathy has historically responded poorly to treatment. Thyroid control appears to have little to do with lesion regression. Corticosteroids under occlusion have been reported to be highly effective. However, as shown in our patient, pragmatically, intralesional steroids may prove to be the most efficacious. Other treatments such as intralesional octreotide, surgical resection, intralesional steroids, and IVIG have been used. Surgery alone is usually not recommended because of a high rate of recurrence.

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Case #15 - Continued

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Case #16

PRESENTED BY: *Sidney Barsky, M.D. and Meredith Stewart, M.D.*

HISTORY OF PRESENT ILLNESS:

This 33-year-old Hispanic male presented with a three-week history of an asymptomatic generalized rash that started on the arms and quickly spread to involve the trunk, back, thighs, neck, and face. The rash started approximately 3 days prior to starting medications for his recently diagnosed HIV infection. The patient denied any history of genital lesions or ulcers, oral ulcers, pain, fevers, chills, headache, nausea, vomiting, diarrhea, myalgias, arthralgias, or urinary symptoms. He did admit to an unintentional 10-pound weight loss over the past 6 months despite a normal appetite, generalized fatigue, and occasional light-headedness without syncope for the past month.

PAST MEDICAL HISTORY:

HIV- diagnosed three months prior to presentation
CD4 count (CD3+CD4+): 219
HIV RNA quant: 293,000
RPR- non-reactive ten weeks prior to presentation
Jaw fracture

MEDICATIONS:

Sustiva (efavirenz)
Combivir (lamivudine/zidovudine)

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

The patient admitted to unprotected homosexual activity. The last sexual contact was 2 months prior to the development of the rash. He denied the use of alcohol, tobacco, or drugs.

Case #16 - Continued

PHYSICAL EXAMINATION:

There was a symmetric and generalized eruption of innumerable erythematous firm round to oval plaques measuring 0.5-2.0 cm, many with a fine white collarette of scale, diffusely and symmetrically distributed on his arms, forearms, chest, abdomen, back, medial thighs, neck, forehead, cheeks, and scalp. The scalp lesions were associated with patchy alopecia. The lesions spared his genitals, palms, and soles. There was an isolated 0.4x 0.5 cm white plaque with ragged borders on the distal aspect of the right lateral tongue. There was no lymphadenopathy.

LABORATORY EXAMINATION:

The following were abnormal or positive:
RPR (Rapid Plasma Reagent): reactive- 1:64
PATP (Passive Particle Agglutination): reactive

BIOPSY:

None performed

DIAGNOSIS:

Secondary Syphilis

TREATMENT AND COURSE:

Given the patient's HIV status, the patient was treated with three weekly doses of Penicillin G benzathine 2.4 million units intramuscularly. One week after the first dose, the rash on the face and neck had almost completely resolved. By the third week, the patient was left with several violaceous to brown macules and patches on his body, and the oral lesion had resolved. The patient had no adverse reactions to the therapy.

DISCUSSION:

See discussion for Case #17.

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Case #17

PRESENTED BY: *Sidney Barsky, M.D. and Meredith Stewart, M.D.*

HISTORY OF PRESENT ILLNESS:

This is a 48-year-old African-American female who was admitted to Cook County Hospital for a four-week history of generalized, pruritic rash that started on the neck and quickly spread to the back, arms, legs, hands, feet, scalp, and genital area. The patient reported recent low-grade fevers and chills, poor appetite and weight-loss. She denied a history of oral or genital lesions prior to the current eruption. She also reported dysuria and was started on Bactrim for a urinary tract infection on the day of admission.

PAST MEDICAL HISTORY:

None

MEDICATIONS:

Bactrim

ALLERGIES:

Penicillin

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

The patient reported a history of poly-substance abuse, including a history of intravenous drug use. She also reported a recent history of unprotected sexual activity.

PHYSICAL EXAMINATION:

There were multiple grayish-brown psoriasiform, scaly, plaques on the arms, legs, chest, scalp, forehead, neck, and back distributed in a symmetric pattern. There were several plaques with raised annular border and central crusted ulceration on the posterior neck, face, and scalp. The

Case #17 - Continued

psoriasiform plaques on the scalp were associated with diffuse patchy alopecia. The palms and soles demonstrated diffuse fine scale and a few <5 mm brown-gray colored scaly plaques. In the genital area, there were multiple coalescent moist, verrucous flesh-colored papules and nodules on the labia, perineum, and perineum. There was palpable lymphadenopathy bilaterally in the occipital and posterior cervical chains; all nodes <1 cm.

LABORATORY EXAMINATION:

The following were abnormal or positive:

HIV 1/ 2 Antibody: positive	Hepatitis B sAb: reactive
HIV Western Blot: positive	Hepatitis B cAb: reactive
RPR: reactive 1:64	Hepatitis C Ab: reactive
PATP: reactive	Hepatitis A Ab: reactive

The following were normal or negative:

CSF chemistry and cell counts	Hepatitis B sAg: non-reactive
CSF VDRL: non-reactive	

BIOPSY:

None performed

DIAGNOSIS:

Secondary Syphilis

TREATMENT AND COURSE:

Given the patient's new diagnosis of HIV infection upon admission, a lumbar puncture was performed to rule out neurosyphilis. This revealed normal chemistries and cell counts and a non-reactive CSF VDRL. Due to her allergy to penicillin, the patient was treated with a 21-day course of doxycylcine at 100 mg PO BID. The patient has been lost to follow-up.

DISCUSSION:

Syphilis is an infectious disease caused by Treponema pallidum (ssp. pallidum), a microaerophilic spirochete that is pathogenic only to humans. There was a steady decline in the incidence of syphilis in Europe and the United States during the second half of the last century, consistently falling every year during 1990 to 2000. According to the CDC, the incidence of primary and secondary syphilis increased 9.1% in 2001 and another 12.4% in 2002 for an average annual incidence of 2.4 cases per 100,000 in 2002. The majority of the increase is seen in men,

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with most of these occurring in men who have sex with men.

Secondary syphilis generally presents 3 to 12 weeks after the appearance of the primary syphilitic chancre, which occurs 18 to 21 days after infection. The secondary stage usually lasts 4 to 12 weeks and is characterized by protean manifestations. Skin manifestations, or syphilids, occur in 80%-95% of cases, and is often the presenting sign. Early eruptions are symmetrical, generalized, and superficial and become polymorphic later in the course. Generally, the eruption involves the face, shoulders, trunk, palms and soles, and anal and genital regions. While the involvement of palms and soles is highly suggestive of secondary syphilis, a generalized syphilid can spare the palms and soles. Most eruptions are macular, maculopapular, papular, or annular. Less frequently, the eruption can be nodular, pustular, or lichenoid. Vesiculobullous skin lesions can be seen in congenital syphilis. Lesions are pruritic in 8%-42% of cases. In all cases, the eruption heals without scarring in 2 to 10 weeks; however, pigmentary changes may remain. Syphilitic alopecia is reported in 5% of cases and the irregular distribution gives a 'moth-eaten' appearance. Mucous membrane lesions, which are extremely contagious, are present in one-third of patients with secondary syphilis and consist of condyloma lata, mucous patches, and pharyngitis. Condyloma lata, reported in 9%-44% of cases, are flesh-colored or hypopigmented, smooth, moist papules found usually in genital and anal areas. They can also be seen on the oral commisures, face, axillae, inframammary folds and toe webs and may become hypertrophic and papillated. Mucous patches, reported in 7%-12% of cases, are painless, shallow, rounded, erosions with gray macerated membrane located anywhere in the mouth, but usually on the tongue and lips. Pharyngitis, which may occur in up to 25% of cases, can be associated with tonsillitis, laryngitis, and hoarseness. Skin and mucous membrane lesions of secondary syphilis may be associated with fever, malaise, headache, myalgias, arthralgias, generalized lympadenopathy as well as a wide array of systemic complications of the ophthalmologic, auditory, musculoskeletal, hematologic, renal, hepatic, gastrointestinal, and central nervous symptoms.

Syphilis and HIV infections can affect similar patient groups and co-infection is common. Syphilis infection facilitates infection and transmission of HIV, probably through the increased incidence of genital ulcer disease. The presentation of syphilis in the HIV-infected patient can have unique features with important diagnostic, prognostic, and treatment implications. HIV-infected patients are more likely to have asymptomatic primary disease and present more often with secondary or latent infection than HIV-negative patients. Secondary disease is more likely atypical, aggressive, and of the ulceronodular type (malignant lues) in the HIV-infected patient. The diagnosis of neurosyphilis is particularly challenging in HIV-infected patients because both syphilis and HIV infection can have neurologic involvement. The incidence of neurosyphilis in HIV infection is increased to 23.5% of those with untreated syphilis compared to 10% in HIV-negative patients with untreated syphilis. In HIV, neurosyphilis can be asymptomatic, or may present with a wide range of clinical signs. It is also suggested that HIV infection accelerates the clinical course and neurologic complications of neurosyphilis. In a recent study, a CD4 count of less than 350 conferred a three-fold increased risk of neurologic involvement in the HIV-infected patient with syphilis. For these reasons, some authorities recommend lumbar puncture and CSF analysis in all HIV-positive patients irrespective of stage of syphilis or symptoms. Alternatively, some think all HIV-positive patients should be given a treatment course to achieve treponemocidal concentrations of penicillin in both the serum and CSF. The Centers for Disease Control and Prevention sexually transmitted diseases treatment guidelines (2002) recommends that early disease (<2 years, primary, secondary, and early latent infection) be treated with

Case #17 - Continued

Benzathine penicillin G 50,000 units/kg IM, up to the adult does of 2.4 million units in a single dose. For early syphilis in HIV-positive patients, the recommended treatment is the same,

Although the guidelines explain that some clinicians recommend 3 doses at weekly intervals, and CSF examination before treatment, with follow-up CSF examination following treatment in persons with initial abnormalities. Additionally, HIV-infected patients should be evaluated clinically and serologically for treatment failure at 3, 6, 9, 12, and 24 months after therapy. Although of unproven benefit, some specialists recommend a CSF examination 6 months after therapy.

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Case #18

PRESENTED BY: *Lissette Ortiz-Ferrer, M.D. and Jane Kwan, M.D.*

HISTORY OF PRESENT ILLNESS:

This 35-year-old Hispanic woman was admitted to the hospital with a two-day history of red, tender nodules on her lower extremities. By day three, she had developed new lesions on her arms and forehead. One week prior to the development of skin lesions, the patient had an upper respiratory tract infection and a sore throat. Her review of systems was significant for fatigue, headache, arthralgias and myalgias. She denied fever, chills, night sweats, weight loss or shortness of breath.

PAST MEDICAL HISTORY:

Bipolar disorder

MEDICATIONS:

Zyprexa (olanzapine)

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

There were tender, warm, erythematous, partially blanching, indurated nodules and plaques measuring 3-5 cm in diameter scattered on the lower extremities bilaterally. A well-defined zone of milder erythema surrounded each lesion. On the forehead and arms, there were 1-2 cm pink to yellow, indurated, edematous papules and plaques. There was no lymphadenopathy present and

the mucous membranes were spared. The patient was slightly febrile with a temperature of 100°F.

LABORATORY EXAMINATION:

The following were abnormal or positive:

White blood cell count	13.0 x 10^9/L	[nl: 3.7-10.5]
Neutrophils	81.8%	[nl: 40-82]
Glucose	454 mg/dl	[nl: 65-110]
Erythrocyte sedimentation rate	111 mm/hr	[nl: 0-30]

The following were normal or negative:

- Antinuclear antibody
- Basic metabolic panel
- Liver function tests
- Throat culture
- Antistreptolysin-O titer
- Hepatitis B and C
- Rapid plasma reagin
- Tuberculin skin test
- Pregnancy test

BIOPSY:

Right arm: There is a dense collection of neutrophils and nuclear dust within the upper reticular dermis. There is also marked edema of the papillary dermis. No fibrin is present within the blood vessel walls.

DIAGNOSIS:

Sweet's Syndrome (acute febrile neutrophilic dermatosis)

TREATMENT AND COURSE:

The patient was started on 40 mg of prednisone daily. After 1 week, her skin lesions had resolved, leaving only post-inflammatory hyperpigmentation. She reported significant improvement of her fatigue, arthralgias and myalgias. The prednisone was tapered down to a dose of 10 mg daily over the course of 1 month. At this point, her symptoms had completely resolved and prednisone was discontinued.

Case #18 - Continued

DISCUSSION:

Acute febrile neutrophilic dermatosis was first described by Robert Douglas Sweet in 1964. Subsequently termed Sweet's syndrome, this entity is characterized by the acute onset of fever, elevated neutrophil count, and erythematous papules, nodules or plaques that are infiltrated by neutrophils.

Classically, skin lesions are tender, sharply marginated, expanding, erythematous plaques or nodules on the face, neck, upper trunk and extremities. Patients will usually complain of a burning or painful sensation in the affected areas as opposed to pruritus. Due to the intense dermal edema, lesions may exhibit pseudovesiculation or, more rarely, true vesiculation or pustulation. Oral lesions are uncommon but appear in the form of aphthous ulcers when present. Lesions involving the lower extremities may resemble erythema nodosum.

Systemic symptoms are present in 75% of patients, the most common being fever, which is found in 50%-80% of those affected, and malaise. Arthritis, arthralgia and myalgias develop in one to two-thirds; eye symptoms, such as conjunctivitis and episcleritis, occur in one-third of patients. Lung involvement can manifest as cough, dyspnea, infiltrates and effusions. Rarely, the heart, kidney, liver, gastrointestinal tract, central nervous system and bones can be affected.

On pathology, an intense nodular or perivascular infiltrate of mononuclear cells and neutrophils is seen in the dermis. Nuclear dust is found along with prominent papillary dermal edema, which can result in subepidermal vesiculation. Vessels in the dermis are dilated, however, there is no evidence of primary vasculitis. Exocytosis of neutrophils can lead to subcorneal pustule formation. Laboratory findings often display an elevated erythrocyte sedimentation rate, neutrophil count and total leukocyte count.

Criteria for the diagnosis of Sweet's syndrome have been delineated. Major criteria include (1) the abrupt onset of tender red plaques or nodules and (2) a neutrophilic infiltrate in the dermis without evidence of leukocytoclastic vasculitis. Minor criteria include (1) a preceding upper respiratory or gastrointestinal infection, vaccination, or association with an inflammatory disease, malignancy or pregnancy; (2) malaise or fever above 38^{o}C; (3) ESR above 20, a positive C-reactive protein, neutrophils above 70%, WBC above 8000 (need 3 of 4); and (4) a rapid response to steroids or potassium iodide. For the diagnosis of Sweet's syndrome to be considered, one major and two minor criteria must be fulfilled.

Sweet's syndrome can be classified into the following groups: the classic form, the drug-induced variant, and those cases associated with malignancy, inflammatory disease or pregnancy. Classic or idiopathic Sweet's syndrome accounts for approximately 71% of all cases. Typically, females between the ages of 30 and 50 years are affected, however, Sweet's syndrome can occur in young adults and children as well. The youngest reported patient was only 7-weeks-old. Often, an upper respiratory tract or gastrointestinal infection precedes the onset of symptoms.

Malignancies can be found in 10%-20% of patients; these include hemoproliferative disorders, such as leukemia and lymphoma, as well as solid tumors of the breast, genitourinary tract and gastrointestinal tract. Patients tend to be older, with males and females being equally affected. Recurrence of symptoms is more common and neutrophilia is less frequently found in comparison to classic Sweet's syndrome. Anemia is demonstrated in 70%-90% of cases along

with thrombocytopenia in 50%. Skin lesions tend to be solitary or ulcerative.

Inflammatory or autoimmune diseases associated with Sweet's syndrome include inflammatory bowel disease, lupus erythematosus, dermatomyositis and Beçhet's disease to name a few. Infections such as tuberculosis, leprosy, yersiniosis and salmonellosis have also been reported to precipitate symptoms. Pregnancy-induced disease tends to develop in the first to second trimester and can recur with subsequent pregnancies. Fortunately, there is no known risk to the fetus.

In the drug-induced variant of Sweet's syndrome, there is a female predominance, and the upper extremities are the favored location of lesions. Neutrophilia is more unusual than in the classic form, especially in patients being treated for neutropenia. The most common offending agent is granulocyte colony-stimulating factor. Other implicated medications include trimethoprim-sulfamethoxazole, all-trans-retinoic acid, hydralazine, furosemide, nitrofurantoin, carbamazepine, diazepam, diclofenac, ethinyl estradiol and levonorgestrel, and minocycline.

Sweet's syndrome is self-limited and can spontaneously resolve without treatment in 5-12 weeks. Treating the underlying cause of paraneoplastic or parainflammatory disease can result in resolution of symptoms. Systemic corticosteroids are the mainstay of treatment, and the response is dramatic and rapid. Constitutional symptoms resolve in several days and skin lesions involute without scarring in a week or so. Dosing starts at 40 mg to 60 mg daily and is gradually tapered down to 10 mg daily over 4-6 weeks. Prolonged courses may be required to prevent relapses. Potassium iodide and colchicine are alternative first line or steroid sparing agents. Dapsone, which is used in the treatment of neutrophil mediated disorders, works effectively as well. There have been case reports of doxycycline, clofazimine, indomethacin, NSAIDS, cyclosporine, thalidomide, and interferon-alpha being used successfully in the treatment of Sweet's syndrome. Disease recurs 30% of the time, most often in pregnancy or malignancy-associated cases.

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Case #19

PRESENTED BY: *Warren W. Piette, M.D., Jerry Feldman, M.D, and Jessie Cheung, M.D.*

HISTORY OF PRESENT ILLNESS:

This 46-year-old woman presented with an eruption of blisters on her head and neck that spread rapidly to her body and oral mucosa. The blisters burn, are itchy, fragile, and worsen upon exposure to sunlight. The patient reports night sweats, malaise, headaches, and joint aches. She denies any new contacts or history of herpes.

PAST MEDICAL HISTORY:

Hypertension
Hypercholesterolemia
Depression

MEDICATIONS:

Premarin
Lovastatin
Atenolol
Fluoxetine
Aspirin

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Cigarette smoker

Case #19 - Continued

PHYSICAL EXAMINATION:

There are many tense straw-yellow 2-4 mm vesicles and pink macules scattered on the neck, face, gluteal cleft, back, proximal extremities, and wrists. There are a few white ulcers on the oral mucosa. On the frontal scalp there is a well-demarcated pink atrophic plaque of scarring alopecia.

LABORATORY EXAMINATION:

The following were abnormal or positive:

Hemoglobin 12.4 (12.5-16.7)
ANA > 1:160, speckled pattern (<1:20)
RNP/Sm 604 (<83)
SSa 246 (<91)

The following were negative or normal:

Basic metabolic panel
liver function tests
G6PD
dsDNA 8 (<40)
Smith 16 (<89)
SSb 13 (<73)
C3 118
C4 17
urinanalysis.

BIOPSY:

There is a subepidermal separation. Neutrophils, nuclear dust, and occasional eosinophils are present within the papillary dermis.

DIAGNOSIS:

Bullous Systemic Lupus Erythematosus

TREATMENT AND COURSE:

The patient was started on topical steroid ointments and sunscreen along with dapsone 100 mg daily. The patient was also started on hydroxychloroquine 200 mg twice daily by Rheumatology. The dapsone was gradually increased to 150 mg daily, with a marked decrease in blisters although new blistering still occurred. Since the patient couldn't tolerate dapsone 200 mg daily, prednisone 20 mg daily was added after the patient had already been on dapsone for 2 months, in

Case #19 - Continued

an attempt to further decrease blistering. The dapsone was stopped after a total 4 months duration when the patient's liver function tests (AST, ALT, GGT) became significantly elevated. The patient noted an increase in blistering off the dapsone. Her liver function tests normalized 3 weeks after stopping dapsone. Sulfapyridine was then started at 250 mg daily and slowly

increased to 250 mg three times daily along with azathioprine 50 mg daily. The patient still notes active blistering; an increase in the dose of azathioprine and sulfapyridine is anticipated.

DISCUSSION:

Bullous lupus erythematosus (BSLE) is a rare subset of systemic lupus erythematosus. Some patients have bullous eruptions related to lupus erythematosus but do not meet the American College of Rheumatology criteria for SLE. BSLE is associated with autoantibodies to type VII collagen resulting in chronic, widespread, non-scarring subepidermal blisters. The eruption is generally unrelated to the severity of the SLE. Approximately 76% of patients with SLE will have skin changes at some stage during the course of their disease. Among these patients, fewer than 5% will have chronic vesicobullous lesions.

Patients with BSLE usually present in the second or third decade of life. They seldom have discoid lesions or annular erythema. Bullous lesions may form on the trunk, or on flexural and extensor surfaces with a preference for sun-exposed areas. The lesions may form on normal skin or an erythematous base. Oral lesions are seen in about 30% of the cases. BSLE lesions generally last for many weeks to months, with remissions and exacerbations, and typically responds dramatically to dapsone. A good response to dapsone correlates with a better prognosis in BSLE; however, discontinuation of dapsone may allow new lesions to develop. The bullous lesions often fail to respond to treatment with systemic corticosteroids alone; adjuvant therapy with azathioprine, antimalarials, colchicine, methotrexate, and cyclophosphamide have been reported to be useful in cases unresponsive to or intolerant of dapsone.

Epidermolysis bullosa acquisita (EBA) shares a common antigen, type VII collagen, with BSLE. EBA usually presents in the fourth or fifth decade of life, with acrally distributed mechanobullous lesions or widespread inflammatory vesicubullous lesions. EBA is more likely than BSLE to result in scarring. Unlike BSLE, EBA is frequently treatment resistant.

The proposed criteria for the diagnosis of BSLE include a diagnosis of SLE, vesicles and bullae located on but not limited to sun-exposed skin, histopathology similar to dermatitis herpetiformis, and deposition of IgG and/or IgM and often IgA at the basement membrane zone on DIF with a granular or continuous granular pattern. On histology, there is typically a dermal-epidermal separation with neutrophil-predominant inflammation in the upper dermis. There are some cases that resemble dermatitis herpetiformis when the infiltrate concentrates in the dermal papillae as microabscesses. Some patients may have circulating IgG antibodies to the DEJ. Electron microscopy localizes the blisters to the lamina densa region. The autoantibodies usually recognize the 290-kd and 145-kd antigens at the DEJ.

Case #19 - Continued

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Case #20

PRESENTED BY: *Jerry Feldman, M.D. and Samantha Golden, M.D.*

HISTORY OF PRESENT ILLNESS:

This 65-year-old Filipino woman presented in August 2004 with a three-month history of a firm, red, 1.7 cm X 1.5 cm, growing nodule on her right cheek. She denied fever, chills, weight loss, change in appetite and the presence of any other lesions.

PAST MEDICAL HISTORY:

Diabetes mellitus

MEDICATIONS:

Metformin

ALLERGIES:

Penicillin

FAMILY HISTORY:

No family history of any type of skin cancers.

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

On the patient's right cheek there was a 1.7 cm X 1.5 cm indurated, red, well-demarcated nodule. There were small superficial telangiectasias overlying the tumor, but no other surface change. There was minimal surrounding erythema. No other lesions were apparent at that time. The patient had no palpable cervical, preauricular, submandibular, submental, or axillary lymphadenopathy.

Case #20 - Continued

LABORATORY EXAMINATION:

The following were normal or negative:
- basic metabolic panel
- complete blood count
- liver function test

BIOPSY:

There is a dermal nodule composed of basophilic cells with scanty cytoplasm and large vesicular nuclei. There are numerous mitotic figures and some nuclear fragments. In some of the areas, the cells are arranged in a trabecular pattern.

The neoplastic cells marked positively for NSE (neuron-specific enolase) and CK 20 (Cytokeratin-20 staining which shows perinuclear capping). The cells stained negatively for pankeratin and LCA (leukocyte comman antigen).

DIAGNOSIS:

Merkel Cell Carcinoma

TREATMENT AND COURSE:

The patient was seen by Surgical and Medical Oncology and subsequently underwent wide surgical excision of the tumor along with lymph node biopsies of the deep jugular, right preauricular, proximal maxillary, base of the skull, posterior cervical lymph nodes, as well as the parotid gland. Two out of four of the parotid gland lymph nodes were positive for merkel cells. All other nodes were negative. The patient subsequently underwent radiation therapy.

DISCUSSION:

Merkel cells were first described by Frederick Merkel in 1875 and are believed to be slow-acting mechanoreceptors in the basal layer of the epidermis related to touch and hair movement. Merkel cells are of neuroendocrine origin and after migration to the skin continue to express several neuronal and epithelial markers. Merkel cell carcinoma is a rare and aggressive form of cancer, first described as Trabecular-cell carcinoma in 1972 by Toker. More than 2,000 cases have since been reported.

The data from the Unite States Surveillance, Epidemiology, and End Results (SEER) program estimates the incidence of Merkel cell carcinoma to be 0.23 and 0.01 for whites and blacks respectively. Merkel cell carcinoma occurs predominantly in older people, having an average age of presentation of 69 years and occurring before the age of 50 in only 5% of cases. The incidence

Case #20 - Continued

appears to be slightly higher in men, about 2-3 males to every female. Merkel cell carcinoma occurs most commonly on sun exposed areas, usually the head and neck. Both sunlight exposure and immunosuppression have been positively correlated with the incidence of Merkel cell carcinoma. Patients with organ transplantation, leukemia, and HIV infection all have been found to have an increased risk. The relative risk in patients with HIV is 13.4 compared with the general population. Arsenic exposures, as well as methoxsalen and UVA treatments have also been implicated.

Merkel cell carcinoma typically presents as a red nodule with a shiny surface, often with overlying telangiectasias. The differential diagnosis includes most other tumors of the skin. Lesions are usually less than 20 mm in diameter and can present with satellite lesions due to aggressive dermal lymphatic spread. Regional lymph nodes are the most common site of metastasis, and metastatic disease is highly predictive of a poor outcome. Regional node involvement develops in 50%-70% of patients within 2 years and is apparent at initial presentation in 12%-31% of patients. Disseminated metastases occur in more than 30% of patients and most commonly involve liver, lung, bone and brain. Spontaneous regression of the primary tumor has been documented, but regression usually incurs a less favorable prognosis. Other factors that predict a poorer prognosis include tumor on a lower limb, male sex, primary size greater than 2 cm, age older than 60, and lack of radiotherapy in management.

Pathologically, Merkel cell carcinoma is usually found in the dermis, but the cells may invade the subcutaneous tissue, the epidermis, as well the surrounding vascular structures. The tumor is composed of ovoid cells that have scanty cytoplasm and plump, round or irregular nuclei. The cells are usually closely spaced in sheets or arranged in a trabecular pattern. Mitotic and apoptotic cells are prevalent. Merkel cell carcinoma is often confused with other poorly differentiated blue-cell tumors, most often small-cell carcinoma of the lung. The nuclei of pulmonary small cell undifferentiated carcinomas, however, are irregular and often have a pointed extremity. Electron microscopy of biopsies of Merkel cell carcinoma reveals fine granular dispersed chromatin and few nucleoli in nuclei of properly fixed specimen. All specimens exhibit the characteristic paranuclear whorls of intermediate filaments. Typically, Merkel cell carcinoma will express both neuroendocrine (neuron-specific enolase, synaptophysin, chromogranin) and cytokeratin markers (CK 20, CAM 5.2) and will be negative for S100 and leukocyte common antigen (LCA). The KIT receptor tyrosine kinase (CD 117) is expressed in 95% of Merkel cell carcinomas, but its presence has no known clinical correlation. Cytokeratin 20 has been proposed as a marker able to differentiate Merkel cell carcinoma from small cell carcinoma of the lung, as the latter is essentially negative for CK 20. Most recently, several studies revealed the value of combined immunostaining with thyroid transcription factor-I and CK 20 to distinguish between the two diseases. Although several chromosomal abnormalities have been elucidated for Merkel cell carcinoma, no specific tumor-suppressor gene or oncogene has definitively been implicated.

There is currently no consensus, and often a lot of confusion, regarding the optimal therapeutic approach for patients with Merkel cell carcinoma. Large, multicentered, randomized, controlled trials are needed to define the role of surgery, Moh's surgery, sentinel lymph node biopsy, elective lymph node resection, radiotherapy, and chemotherapy in the treatment of patients with this disease. Treatment of Merkel cell carcinoma is very difficult because these tumors have a highly malignant potential for local recurrence, nodal spread, and distant metastases. The currently recommended treatment for localized disease has been surgical excision of the primary

Case #20 - Continued

lesion, with a wide margin of 2 cm-3 cm. Current trials suggest Mohs microsurgery may allow for a complete removal of the primary lesion with smaller margins. However, loco-regional recurrence after surgery is common and failure to control the primary site has demonstrated the correlation with the development of regional and distant metastases. Merkel cell carcinoma is radiosensitive. Most investigators have shown an improvement in relapse-free survival when adjuvant loco-regional radiotherapy was applied, however, a benefit in overall survival has only been demonstrated in a few series. Chemotherapy has a well-defined role in metastatic disease, but responses are usually short-lived and all patients ultimately succumb to the disease. The 5-year survival rates of stage I and II disease are about 64% and 47%, respectively. Stage III disease has a dismal prognosis of only 9 months.

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Case #20 - Continued

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Case #21

PRESENTED BY: *Sidney Barsky, M.D. and Shirley Chi, M.D.*

HISTORY OF PRESENT ILLNESS:

This 25-year-old woman presents with thickening of the palms and soles which began when she was approximately one-year-old.

PAST MEDICAL HISTORY:

Bilateral sensorineural hearing loss, onset at age 9 months

MEDICATIONS:

None

ALLERGIES:

None

FAMILY HISTORY:

Non-contributory

SOCIAL HISTORY:

Non-contributory

PHYSICAL EXAMINATION:

Yellow hyperkeratotic plaques on bilateral palms and soles, not crossing line of transgredience; firm, rubbery plaques overlying metacarpal-phalangeal joints on dorsae of hands; normal dentition, visual acuity, and hair.

LABORATORY EXAMINATION:

None indicated

BIOPSY:

None performed

DIAGNOSIS:

Palmoplantar Keratoderma with knuckle pads and deafness: Bart-Pumphrey Syndrome

TREATMENT AND COURSE:

Tazarotene 0.1% gel and clobetasol ointment were initiated in November 2004.

DISCUSSION:

The inherited palmoplantar keratodermas(PPK) are rare disorders and our knowledge of them is based mostly on case reports of individual families, resulting in numerous disease eponyms and non-uniform categorizations. A recent classification which is relatively straightforward divides keratodermas into 3 types based on morphology and distribution of the lesions: diffuse, focal, and punctate PPK. Among the diffuse PPKs are certain types that present with associated features, such as Vohwinkel's syndrome, Clouston's syndrome (hidrotic ectodermal dysplasia), Olmstead's syndrome, Papillon-Lefevre syndrome, Naxos syndrome, and what we believe this patient to demonstrate, Bart-Pumphrey Syndrome.

Bart-Pumphrey syndrome is characterized by sensorineural hearing loss, palmoplantar keratoderma, knuckle pads, and leukonychia. Although it is thought to be an autosomal dominant disorder, few sporadic cases have been reported. The clinical features partially overlap with Vohwinkel syndrome and Keratitis-Ichthyosis-Deafness syndrome, all of which have been shown to be caused by dominant mutations in the gap junction B2 (GJB2) gene encoding gap junction protein connexin-26 (Cx26). Thus, an etiologic relationship has been postulated between all three disorders. In addition, Martin et al. reported a family with PPK and sensorineural hearing loss that was associated with a A7445G point mutation in the mitochondrial genome. Expression of the other epidermal proteins, including keratins, loricrin and Cx26, was normal, making it the only type of keratoderma associated with a mutation in mitochondrial DNA.

Human connexins are a multigenic family of 20 structural proteins forming gap junctions, clusters of intercellular channels that permit the diffusional exchange of ions and small molecules between adjoining cells. Genetic studies have linked mutations in connexin genes with a spectrum of disorders including hearing loss, neuropathy, cataracts, and a number of skin

disorders. The principle connexins in the skin are Cx26 and connexin 43. Cx26 is widely expressed in most tissues of the human body, including the cochlea, cornea, and skin. The complete loss of Cx26 protein or its function due to recessive mutations in GJB2 is the singlemost common cause of non-syndromic sensorineural hearing impairment with high carrier frequencies from 3%-10%. Although Cx26 is not expressed on normal mature keratinocytes, it has been found in the hyperplastic epidermis of lesional psoriasis, basal cell carcinoma, chronic wounds, viral warts, and in the physiologic hyperproliferation of both vaginal and buccal epithelium. Cx26 mutations associated with palmoplantar keratodermas disrupt intercellular conductance of coexpressed connexin 43 and thus may exert their skin phenotype in part through their negative effect on connexin 43.

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