CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

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Case # 1

CHICAGO DERMATOLOGICAL SOCIETY
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CASE PRESENTED BY: Michael D. Tharp, M.D. and Alix J. Charles, M.D.

History: This 51 year old white male was referred to our department for evaluation and treatment of a burning and pruritic erythematous eruption of seven months duration. The patient reported that lesions would appear on the trunk and extremities and last for more than twenty-four hours before resolving with hyperpigmentation. The eruption was also associated with swelling and joint pain of the hands. Treatment with zyrtec, allegra, clarinex, atarax, and medrol dose packs had been met with little success.

Past Medical History: Family history of systemic lupus (daughter). Otherwise unremarkable.

Physical Findings: The extremities, chest, and back display dozens of discrete and confluent erythematous and purpuric, non-blancheable macules and plaques. Some lesions have an annular configuration. The patient's palms displayed violaceous plaques that were tender to palpation.

Laboratory Data: November 2002: 24 Hr Urine protein – 227 (nl <150), Hgb 11.8, Wbc 2.5, ESR 80, RF negative, ANA 1:160, SPEP- broad increase in gamma region, no monoclonal peak. Hepatitis screen, complements, complete blood count, and complete metabolic panel were otherwise within normal limits.

Biopsy Description: Left arm- Edema of the papillary dermis. There is a dense diffuse neutrophilic inflammation with surrounding nuclear dust, lymphocytes and eosinophils. Although fibrin is not seen, urticarial vasculitis must be considered.

Direct Immunofluorescence- Focal and weak IgG in epidermal nuclei, areas of granular C3 in junctional region, and a focus of non-disease specific fibrin deposits in upper reticular dermis. Questionable positive in situ ANA and LE band test.

Diagnosis: **Urticarial Vasculitis**

Present Course and Therapy: The patient was started on prednisone 40mg qd and plaquenil 200mg bid. After normal serum levels of G6PD were confirmed, prednisone was increased to 60mg qd and dapsone 50mg qd was added. Due to the continuing development of new lesions, the dose of dapsone was increased to 100mg qd. Slowly, the patient began showing signs of improvement. During the first five months of treatment the dose of prednisone was gradually reduced to 35mg qd and the plaquenil was discontinued. Following two months of improvement, the prednisone dose was further reduced while the dapsone dose was decreased to 75mg qd. After six months of dapsone therapy and two months without new lesions, the dapsone was

discontinued due to continued complaints of leg and foot pain. The patient is currently lesion free on a maintenance dose of prednisone 5mg qod.

Discussion: Urticarial vasculitis (UV) is an entity that is differentiated clinically from urticaria by erythematous wheals that burn rather than itch, and last longer than 24 hours before resolving with hyperpigmentation. The histopathologic picture is one of leukocytoclastic vasculitis indicating damage to dermal capillaries and post-capillary venules. UV is not a diagnosis per se, but rather represents a clinicopathologic entity that occurs idiopathically or in association with a systemic disease. Connective tissue diseases (SLE. Sjogren's), infections (Hepatitis B and C, EBV, Lyme disease), complement deficiencies, immunoglobulin abnormalities and rarely drugs (diltiazem, cimetidine, fluoxetine) have all been reported as causative factors.

The majority of UV patients are women who present in middle age. Urticarial wheals can occur anywhere, vary in size, and tend to persist for three to four days. Associated angioedema has been reported to occur in up to 42% of cases. Systemic manifestations are also commonly seen, with arthralgia and abdominal pain affecting 50% and 20% of patients, respectively. Obstructive pulmonary disease, microhematuria and proteinuria, fever, conjunctivitis, uveitis and even pericardial effusions have also been reported. The histology of many UV lesions displays endothelial cell injury and swelling, leukocytoclasis, extravasation of red blood cells, and fibrin deposition. Fibrinoid change, necrosis and thrombosis, however, are not seen as commonly as they are in lesions of palpable purpura.

There are no randomized trials of treatment for UV, and individual response to therapy shows variation. Antihistamine therapy alone is usually ineffective. Most patients benefit from systemic corticosteroids, although long term use may be limited by side effects. Indomethacin, colchicine, dapsone, cytotoxic agents and antimalarials have all been used with various levels of success.

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Case # 2

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MAY 19, 2004

CASE PRESENTED BY: James O. Ertle, M.D. and Rachel S. Altman, M.D.

History: This 22 year old Hispanic female with a past medical history of Lupus anticoagulant and deep venous thrombosis presented with a very pruritic, slightly painful rash that began on her chest on 1/1/04 and progressed over the next week to involve her entire trunk and all four extremities, sparing the face, acral surfaces and mucosal surfaces. She denied fever or chills or change in energy level or appetite.

Past Medical History: Lupus anticoagulant
Deep Venous Thrombosis

Physical Findings: Generalized annular erythematous indurated plaques with superimposed pinpoint 1-2 mm pustules, with some desquamation.

Laboratory Data: ANA<1:40, RPR non-reactive, Liver function tests within normal limits, WBC 14.9 K/uL (4.8-11.8) with 64% Neuts, 31% lymphs, 4% Mono, 1% Eos, 1% Baso; Hgb/Hct, platelet, electrolytes, BUN/Creatinine, glucose all within normal limits; G6PD 218 (146-376)
Serum & Urinary Protein Electrophoresis – Pending.

Biopsy Description: 1/13/04 (L mid-back) – Subcorneal and intracorneal pustular dermatosis suggestive of Sneddon Wilkinson Disease. The epidermis revealed irregular psoriasiform hyperplasia with overlying skip areas of orthokeratosis and subcorneal pustules containing numerous neutrophils. Papillary dermis showed mild perivascular mixed cell infiltrate consisting of lymphocytes, histiocytes and few neutrophils. Blood vessel walls were intact with no evidence of vasculitis.

1/13/04 (L mid-back) – Intracorneal pustular dermatitis. Epidermis revealed mounds of intracorneal collections of neutrophils and serum crust. There was irregular psoriasiform hyperplasia of the epidermis. The papillary dermis revealed mild perivascular mixed cell infiltrate consisting of lymphocytes, histiocytes and few neutrophils.

Diagnosis: **Subcorneal Pustular Dermatosis** (Sneddon Wilkinson Disease)

Present Course and Therapy: A diagnosis of subcorneal pustular dermatosis is most consistent clinically and histopathologically. Previous to visiting RUSH, the patient was placed on Prednisone and Plaquenil with no relief. She was started on triamcinolone 0.1% ointment bid followed several days later with Dapsone 25-50 mg day. Patient noted almost complete remission within 2-3 days after starting Dapsone therapy (at 25 mg per day). Therapy was successfully tapered over an eight week course. Currently, she is symptom free and without recurrences (without Dapsone).

Discussion: Sneddon-Wilkinson disease (first described by Sneddon and Wilkinson in 1956) is a rare chronic, benign, relapsing vesiculopustular eruption that usually involves the axillae, groin, abdomen, and flexural proximal extremities of middle aged women. This disease more commonly affects women and adults, however it can affect all ages including children with no racial preference. The first case may have been an Egyptian mummy who died in 892 BC +/-53 years who was found with well-preserved skin that revealed inguinal subcorneal vesicles of the type seen in subcorneal pustular dermatosis.

The exact pathogenesis is unknown however several speculations exist:

1) Hyperactivation of neutrophils in the skin with migration of neutrophils toward the epidermis may be secondary to excessive production of tumor necrosis factor alpha. In a case report of a single patient, increased levels of TNF alpha production by monocytes lead to elevated levels of TNF in pustules (>serum). The only effective treatment in this case was corticosteroids, which happened to be the only treatment that affected TNF production (thereby decreasing TNF levels in serum and pustules), unlike dapsone and plasma exchange. This theory also supported by the effectiveness of Infliximab (a chimeric anti-TNF alpha antibody).
2) Immune complex and complement deposits may provide a chemotatic gradient for the accumulation of neutrophils and pustule formation.

Diagnostic Criteria have been proposed (must have at least 4 of 5): 1) New onset of pustular eruptions without systemic symptoms, 2) Flaccid pustules with pus filling the lower half, 3) Absence of existing psoriasis or other stigmata of psoriasis, 4) Subcorneal neutrophilic pustule without spongiosis, 5) Response to dapsone if challenged.

Primary lesions consist of a pustule that arises on normal or mildly erythematous skin. The pustules readily rupture and form superficial crusts. Lesions coalesce to form annular or circinate patterns. Healed pustules leave hyperpigmentation. Pain or pruritus is rare. No systemic symptoms are present. Most commonly involves the abdomen, flexor limbs, axillae or neck. Palms, soles, face or head are rarely involved.

Pathology reveals an accumulation of subcorneal neutrophilic abscesses separated from a non-specific epidermis with or without acantholytic cells. The pustules are sterile. Usually a mixed superficial perivascular infiltrate is present. Direct and indirect immunofluorescence are negative.

Sneddon Wilkinson has been associated with IgG cryoglobulinemia, IgA paraproteinemia, IgA and IgG myeloma (rule out by screening urine and serum for paraproteins), pyoderma gangrenosum, apudoma, metastatic epidermoid carcinoma of lung, rheumatoid arthritis, systemic lupus erythematosus, localized bullous pemphigoid & morphea, amicrobial lymph node suppuration & aseptic spleen abscesses, multiple sclerosis, hyperthyroidism, inflammatory bowel disease (Crohns), and subcorneal IgA pemphigus.

The differential diagnosis includes Sneddon Wilkinson (subcorneal neutrophils, acantholytic cells and eosinophils rare), dermatitis herpetiformis (papillary collections of neutrophils and eosinophils, dermal “nuclear dust”), impetigo (subcorneal neutrophils, few acantholytic cells, occasional bacteria), glucagonoma –necrolytic migratory erythema (eosinophilic, necrotic malpighian layer leading to cleft formation, secondary neutrophil infiltration), pemphigus foliaceus (prominent epidermal acantholysis, dyskeratotic granular cells, eosinophilic spongiosis may be present), pustular psoriasis (neutrophils

collect in the malpighian layer, parakeratosis present, neutrophils seen emanating from capillaries) and subcorneal IgA pemphigus (autoantigen desmocollin 1).

Treatment of choice is dapsone, which is usually effective within 1-4 weeks. Maintenance treatment is usually required secondary to relapses upon withdrawal. Patients need close monitoring for possible methemoglobinemia or hemolytic anemia possibly requiring discontinuation. Other treatment modalities include corticosteroids, retinoids (Etetrinate, Acitretin), PUVA or narrow band UVB, Vitamin E, Cyclins, Colchicine, plasma exchange, topical retinoids and corticosteroids (for localized lesions), chemotherapy (if patients has an underlying myeloma), Infliximab (chimeric anti-TNF alpha Ab) at 5mg/kg.

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Case # 3

CHICAGO DERMATOLOGICAL SOCIETY
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MAY 19, 2004

CASE PRESENTED BY: Mark D. Hoffman, M.D., Lady C. Dy, M.D., and Michael K. O'Donoghue, M.D.

History: This 35 year old white man presented in September of 2003 with a six month history of multiple blue lesions erupting on his chest, back, arms, legs and face. The patient had first noted a dark spot on his upper left back early in 2003 which had been biopsied and interpreted as a blue nevus. A review of systems was notable for increased tiredness, dyspnea on exertion, anorexia, abdominal bloating, night sweats and a 15-pound weight loss.

Past Medical History: There was no personal or familial history of skin cancer.

Physical Findings:
Chest, back, arms, axillae, legs, face, hard palate - 75-100 0.3-1.0 cm blue-grey to violaceous papules and nodules
Lymph nodes - palpable cervical and axillary nodes
Right Testicle - enlarged with 3-4 firm, immobile nodules
Hepatomegaly

Laboratory Data:
WBC 4.1, Hgb 10.9, Hct 33.2, PLT 121 with (87% PMN, 40% bands, 3% lymphs, 8% mono); LDH 2232, Total prot 4.7, Albumin 2.4, T bili 1.4, D bili 0.9, Alk phos 73, SGOT 49, SGPT 60
CT Abdomen: numerous cystic lesions in the liver, an approximately 7cm solid mass in the left lobe of the liver, and multiple cystic areas in both kidneys
Bone Scan: increased uptake in L1 and left femur
CT Brain: small area of hypodensity in the region of the left basal ganglia
Abdominal ultrasound: two solid masses in the liver, multiple cysts in the kidneys, splenomegaly

Biopsy Description:
08/08/03: Left Back – Pigmented epithelioid melanocytoma (animal/equine melanoma): reveals a nodular mid-dermal infiltrate, consisting of atypical melanocytes, containing heavily pigmented dark brown globules. There is focal accentuation around the adnexal structures.
10/23/03: Right Testicle (orchiectomy) - metastatic melanoma

Diagnosis: **Animal-Type Melanoma**

Present Course and Therapy: The patient received two courses of interleukin-2 therapy in November and December of 2003. The patient expired in April 2004.

Discussion: Melanoma metastatic to the skin simulating blue nevi is a rare event with only a few cases reported in the literature. Busam reported three cases in which a primary melanoma was found and within three years the patients presented with multiple eruptive pigmented lesions all of which were 0.5-1.0 cm and appeared as dark and bluish. In these cases, the blue-nevi-like metastases occurred in the same anatomical region as the primary tumor.
Wieselthier and White presented a case of multiple blue nodules on the nasolabial fold, axillae, upper arm, forehead and scalp in a women who had a previous diagnosis of ocular melanoma. The initial skin lesion found on the nasolabial fold was reported as a benign blue nevus. Subsequent lesions were consistent with metastatic melanoma. The patient later developed liver and lung metastases.

Finally, animal type melanoma is a rare dermal-based melanocytic neoplasm with prominent pigment synthesis that mimics melanocytic neoplasms seen in horses and laboratory animals, and can present with blue-black nodules. Crowson et al. presented six cases in which lesions with irregular borders from 1.0 to 4.0 cm in size were located on the scalp, lower extremities, back and sacrum. Only one patient died of the disease with widespread visceral metastasis while the other patients are alive and well. The authors believe that the disease usually follows a benign course, but given the rarity of the disease, the behavior is unpredictable. The histology showed prominent dermal involvement with confluent sheets of heavy melanized cells that extended to the dermal subcutaneous interface without a significant grenz zone of papillary dermal sparing. The nuclei of the melanocytes were large with irregularly thickened membranes, coarse chromatin and prominent nucleoli.

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Case # 4

CHICAGO DERMATOLOGICAL SOCIETY
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CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Michael D. Tharp, M.D. and Kelle L. Berggren, M.D.

History: This 28 year old man presented to Rush with a 5 year history of multiple lesions on his right abdomen. While new lesions appeared over six months in the same general area, old lesions flattened leaving hyperpigmented macules. There was no preceding trauma to the area. He complained of mild pruritus, but not pain, and cosmetic concerns. The course of the lesions was unchanged despite Elidel and mid to high potency topical steroids. An excisional biopsy was performed.

Past Medical History: The patient is healthy. His mother has a history of a desmoid tumor.

Physical Findings: A cluster of reddish brown indurated papules was noted on the patient's right abdomen and flank. There were also hyperpigmented macules intermixed.

Laboratory Data: None

Biopsy Description: 10/25/02: Increased number of fibrocytes with course collagen bundles arranged randomly consistent with dermatofibroma.
4/21/03: Dermatofibroma, no involvement of subcutaneous tissue.
10/10/03: Dermal spindle cell proliferation which stain positive for vimentin, smooth muscle actin and CD34. Scattered CD68 positive cells are noted. S-100 stain was negative. A possibility of DFSP was raised.
10/22/03: Dermatofibroma. Outside consultation with Dr. Thomas Krausz at University of Chicago agrees with this conclusion.
1/02/04: Dermatofibroma consisting of a dermal paucicellular proliferation of spindle cells. Extends focally into adipose tissue. Some of the spindle cells react with CD34 and Factor XIIIa. A few spindle cells are positive for SMA. Caldesmon is negative.

Diagnosis: **Multiple Clustered Dermatofibromas**

Present Course and Therapy: A diagnosis of a benign cluster of dermatofibromas is most consistent clinically and histopathologically. However, based on the unusual nature of the lesions, a relatively benign dermatofibromasarcoma protuberans cannot be ruled out. The lesions are being closely followed and complete surgical removal is being considered.

Discussion: Dermatofibroma (DF) is a common benign fibrohistiocytic tumor. It is seen primarily in adults and favors the lower extremities but may arise in any location. They are firm, minimally elevated to dome-shaped papules that usually measure from a few millimeters to 10 millimeters in diameter. A useful clinical feature is the "dimple or Fitzpatrick's sign": when the overlying epidermis is squeezed, there is tethering of the skin to the underlying

dermis. Initially dermatofibromas were thought to arise as a result of a stimulus to the skin, such as an insect bite, although this theory has been challenged. It is now thought that the dermatofibroma is either a tumor of the dermal dendrocyte or an abortive immunoreactive process, featuring dermal dendritic cells as the initiators of disease.

Multiple eruptive dermatofibromas are a rare condition reported in patients with autoimmune and neoplastic diseases, with and without immunosuppressive treatment, HIV infections and other conditions including hydronephrosis, diabetes, hypercholesterolemia, obesity, atopic dermatitis, and pregnancy. All of these conditions affect the immune status, suggesting that altered immunity may play a role in the pathogenesis. A role of infectious agents, such as mycobacteria, has been proposed in the genesis of multiple eruptive dermatofibromas in HIV-infected patients.

Despite the rarity of multiple disseminated lesions, multiple *clustered* dermatofibromas (MCD) on a single region of the anatomy are rarer still. In 1984, Dupre et al reported the first case of multiple clustered dermatofibromas. To date, approximately twelve cases have been reported in the literature. Most cases are found on the lumbar region and thighs. In most, small lesions clump together and only converge with others at discrete points. A frequent feature of MCD is their linear arrangement. In all reported cases, the lesions appear during the first and second decades of life.

A confounding factor in the differential diagnosis (both clinical and histological) of a dermatofibroma is its resemblance to dermatofibrosarcoma protuberans (DFSP). In dermatofibromas, there is less cellular density, nuclei are smaller and lack atypia, and the cellular pattern tends to follow a less storiform arrangement than in DFSP. It has been reported that staining for factor XIIIa and CD34 may be helpful in distinguishing DFSP from DF. DFSP is negative for factor XIIIa and positive for CD34, whereas DF is positive for factor XIIIa and negative for CD34. However, previous studies showed that some DFs are positive for CD34 (12.5-40% with focal immunoreactivity). In these reports, the CD34 positive areas in DFs showed high cellularity.

References:

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Case # 5

CHICAGO DERMATOLOGICAL SOCIETY
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MAY 19, 2004

CASE PRESENTED BY: Lady Christine C. Dy, M.D. and Kelle L. Berggren, M.D.

History: This 19 year old female presented to our clinic in March 2004. She had a history of "red, scaling plaques" since 6 months of age which were initially misdiagnosed as a diaper rash. Since then, she has seen numerous dermatologists (National Institute of Health, Mayo and Northwestern) who diagnosed her as having Erythrokeratoderma Variabilis. She has been treated with numerous topical and oral medications over the years. Of note, she has undergone multiple trials with Accutane at 60 mg a day and Soriatane at 50 mg a day tapered down to 25 mg per week. The retinoids help initially but seem to lose their efficacy after several months.

Past Medical History: In the past, while the patient was taking Accutane, a diagnosis of focal segmental glomerulosclerosis was made by kidney biopsy after the patient developed hypertension. No clear association was made between Accutane and the kidney disease. She is being treated with Enalapril and cyclosporine currently for her hypertension and kidney disease by nephrology.

Physical Findings: Erythematous, sharply marginated scaling plaques are present on the patient's trunk and extremities. In addition, hyperpigmented, well-circumscribed, hyperkeratotic plaques are present over her lower back, elbows and knees.

Laboratory Data:

Hemoglobin 15.3	Cholesterol 165	Triglycerides 133
AST 12	ALT 27	DEXA scan normal
Complete metabolic Panel normal		

Biopsy Description: Buccal swab years ago consistent with Erythrokeratoderma Variabilis per patient's mother.

Diagnosis: **Erythrokeratoderma Variabilis**

Present Course and Therapy: The patient is being maintained on Soriatane 25 mg twice a day and penicillin 250 mg once a day. Tazorac 0.1% cream is being applied to the hyperkeratotic areas with some relief. She is being monitored for osteoporosis every year with DEXA scans.

Discussion: Erythrokeratoderma variabilis (EKV) is a rare genodermatosis first described by Mendes da Costa in 1925. The hallmark of EKV is characterized by the co-existence of distinctive lesions with two morphologic features. The erythematous component is manifested by bright red to brownish, sharply marginated patches, variable in intensity and shape, which may change their distribution patterns within minutes, hours or days, and be aggravated by

exposure to wind, cold, heat or emotional disturbance. In about 35% the erythema is preceded or accompanied by a burning sensation. The other diagnostic feature is the independent occurrence of yellowish-brown, sharply marginated hyperkeratotic plaques with a ridged or verrucous surface with scale. These plaques may develop on previously erythematous areas or on normal skin. About half exhibit keratoderma of the palms and soles. The erythematous and hyperkeratotic lesions may occur anywhere on the body, but the most common sites of involvement are the face, buttocks, and limbs. There is no disturbance in the growth of hair, nails or teeth.

The erythematous component is most prevalent during childhood and later slowly subsides. In general, the lesions first develop some months after birth with 90% presenting within the first year of life. However, approximately 30% have lesions present at birth. The course of EKV is chronic with gradual progression throughout infancy and childhood but tending to stabilize after puberty. Improvement and periodic clearing of the skin are not unusual. Hormonal influences have been suggested with reports of resolution of lesions at menopause and deterioration during pregnancy or contraceptives. EKV is not generally related to other congenital defects and the health of the patient is not affected. EKV can have a tremendous psychosocial impact on the patient.

Histopathologic features are non-specific and include orthokeratotic hyperkeratosis, moderate to severe acanthosis with a prominent granular layer, papillomatosis, dilated elongated capillaries and very little perivascular inflammation.

EKV is an autosomal dominant keratinization disorder with marked variability of expression. More than 200 cases have been reported to date. Most families with EKV show mapping to chromosome 1p34-p35, and recently the causative gene *GJB*3 encoding Connexin 31 and 30.3 has been identified. Connexins are a family of polypeptides that form the subunits of the gap-junction channels between adjacent cells that functionally allow rapid transfer of ions and second messenger molecules permitting a coordinated response to external stimuli. This communication is crucial for growth control, differentiation and maintenance of tissue homeostasis.

EKV shares many clinical features with progressive symmetric erythrokeratoderma (PSEK) making it difficult to distinguish the two. In contrast to EKV, hyperkeratotic plaques in PSEK usually develop on an erythematous base and the migrating red patches are absent. Netherton Syndrome is also in the differential diagnosis; however, there are no hair shaft abnormalities or eczematous lesions.

Treatment is simple emollients and topical keratolytic preparations usually results in some improvement of the hyperkeratosis. Both topical and systemic retinoids have also been demonstrated to produce marked or complete clearance in most but not all patients. Rapid relapse on discontinuation of retinoids is the rule. Avoidance of trauma to the skin might be beneficial.

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Case # 6

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MAY 19, 2004

CASE PRESENTED BY: Arthur R. Rhodes, M.D. and Michael K. O'Donoghue, M.D.

Diagnosis: **Unknown**

Case # 7

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CASE PRESENTED BY: Arthur R. Rhodes, M.D. and Darrell W. Gonzales, M.D.

History: This 3 year old girl presented with a history of short sparse hair since birth. She has also had several hospital admissions during infancy for episodes of extremely high fever, notable for absence of sweating. Only recently has she begun to have mild perspiration following significant physical exertion. She had an uncomplicated childbirth and has reached all of her developmental milestones. She has no personal history of eczema.

Past Medical History: Her medical history is otherwise unremarkable.

Family History: The patient's parents and two male siblings (ages 8 months and 5 years) are reported to be healthy and without significant medical problems. The maternal grandmother is reported to have an absence of hair on her arms and legs as well as "unusual teeth." A maternal aunt is also reported to have an absence of body hair.

Physical Findings: The patient has short, curly, sparse, light-brown hair. She has a prominent forehead, low-set ears, and a short nose with a low nasal bridge. Her palate was normal. Primary dentition was notable for prominent space between individual teeth and conical shape. Although her fingernails were short, there was no evidence of hyperconvexity of the nail plate. There was no palmoplantar keratoderma.

Laboratory Data: Dental X-rays demonstrated evidence of secondary dentition developing normally.
A sweat test showed normal volume, and normal sodium and chloride concentrations.

Diagnosis: **Hypohidrotic Ectodermal Dysplasia** (Christ-Siemens-Touraine syndrome)

Discussion: Hypohidrotic ectodermal dyplasia (HED) is characterized sparse or absent hair, missing or peg-shaped teeth, and relative inability to sweat. The most common form is X-linked, but both autosomal dominant and recessive forms have been identified. HED is found in all racial groups and in all areas of the world. The X-linked form of HED occurs in approximately 1 in 100,000 live-born boys. The autosomal dominant and recessive forms are less common.

The gene locus for the X-linked form of HED (ED1), located on chromosome Xq12-q13.1, encodes for a ligand called ectodysplasin, expressed by keratinocytes, hair follicles, and sweat glands. The receptor for ectodysplasin (ectodysplasin-A receptor, EDAR) is found on epithelial cells. Mutations in this receptor cause either autosomal recessive or autosomal dominant HED. A new X-linked condition characterized by hypohidrotic ectodermal dysplasia and immune defects (HED-ID) has recently been identified, with the defect in the gene NEMO. Although not readily available, clinical molecular testing is available for ED1, EDAR, and NEMO genes.

Affected newborns may present with a collodian membrane or with marked skin scaling. Scalp hair is sparse to absent at birth, and when present, is usually blonde. Hair may darken at puberty, and secondary sexual hairs may be normal. Body hair is typically reduced or absent. Most male patients are unable to sweat, leading to impaired thermoregulation and recurrent episodes of hyperthemia. Atopic dermatitis is associated in up to two-thirds of affected male patients. Nails of these patients are typically normal.

Abnormal primary and secondary dentition in patients with HED is characteristic. Anodontia, oligodontia, and peg-shaped teeth have been described. Affected individuals also have alterations in their facial appearance including frontal bossing, low-set ears, saddle nose, and full everted lips.

Affected males with HED frequently have extremely thick nasal secretions and cerumen, resulting in recurrent upper and lower respiratory tract infections, gastroesophogeal reflux, and feeding problems. Given the predisposition to hyperthermia, difficulty feeding, and respiratory tract infections, 30% of affected male patients with X-linked HED die within the first two years of life.

Although female carriers for the X-linked form of HED may have full-blown clinical features, most carriers have no evidence of disease. Some female carriers may have only partial involvement with patchy sparseness of hair, a few peg-shaped or missing teeth, and a patchy distribution of sweat glands along the lines of Blaschko. Several case reports have documented that the hypohidrosis of affected female patients improves with age, masking their carrier status. It is important for carrier females to be aware of their 1 in 4 risk of having an affected child in order to anticipate potential needs of the newborn.

There is currently no available "routine" diagnostic test to determine either the more common X-linked HED or its autosomal dominant and recessive forms. Careful clinical examination and family history are the usual means for diagnosis and determination of inheritance transmission. Female heterozygote carriers may be identified by dental abnormalities, mild hypohidrosis, and mild hypotrichosis. HED is not a condition for which a biopsy is necessary or specifically diagnostic. The starch-iodine sweat test is a simple, non-invasive method for confirming the diagnosis and is a useful tool in isolated patients for differentiating homozygous females with autosomal recessive HED from heterozygous females with X-linked HED. After a 2% starch iodine is painted on the backs of patients, they are placed into a heated room. A heterozygous female carrier will demonstrate a mosaic distribution of functional sweat glands. Other forms of ectodermal dysplasia can be distinguished by the differences in the ectodermal structures involved (e.g. hyperconvex nails, palmoplantar keratoderma).

For HED patients who have reduced sweating, treatment focuses on controlling ambient temperatures to prevent hyperthermia. Dental restoration is crucial, with the availability of denture fitting, by the age of three. Otolaryngologic treatment for thick nasal secretions, asthma, and recurrent infections is an important intervention. Associated eczematous dermatitis may require care. Genetic counseling for heterozygous female carriers is essential for affected kindreds.

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Case # 8

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Michael D. Tharp, M.D. and Alix J. Charles, M.D.

History: This 41 year old African American woman presented with a nine month history of brown "streaks" and itchy violaceous papules on her right back, chest, and leg. The patient states that she first developed the violaceous papules and that as these lesions began to fade, they were replaced by brown speckled asymptomatic lines. She denied any personal or family history of a similar eruption. The papules and brown streaks were treated with elidel, protopic, and various potencies of topical steroids with minimal improvement in the symptoms only.

Past Medical History: Depression, treated with effexor. This drug was discontinued one month prior to the onset of her eruption.

Physical Findings: Right back: grouped hyperpigmented and violaceous papules

Right lateral chest: whorled and speckled hyperpigmented patch

Right lower extremity: linear and speckled hyperpigmented patches extending from the upper thigh to the great toe. Some violaceous papules are also seen within the hyperpigmented patch. The great toenail appears dystrophic.

There are no lesions present on the left side of the patient's body.

Laboratory Data: Hepatitis C virus antibody negative.

Biopsy Description: Right Chest: mildly acanthotic epidermis with elongation of the rete ridges and increased basal pigmentation. The papillary dermis reveals numerous melanophages and a mild perivascular lymphohistiocytic infiltrate.

Right Thigh Papule: the epidermis exhibits focal areas of parakeratosis and acanthosis with hypergranulosis. There is a band-like lichenoid infiltrate consisting of numerous lymphocytes and many eosinophils.

Diagnosis: **Linear Lichen Planus**

Present Course and Therapy: Treatment of the violaceous papules with cordran tape has led to some decrease in size and symptoms. The patient is contemplating a trial of intralesional kenalog.

Discussion: Lichen planus (LP) is an inflammatory disorder of unkown etiology. It is clinically characterized by pruritic violaceous papules and plaques, oftentimes distributed along the flexor surfaces. An association between this disorder and hepatitis C infection is noted in

some patient. Several variants of LP have been described including hypertrophic, atrophic, ulcerative, and linear subtypes.

Linear LP is uncommon and represents 0.24 – 0.62% of all patients with LP. It is seen more commonly in Japan. It typically presents as solitary or multiple hyperpigmented macules and violaceous papules arranged in streaks or bands on the torso or extremities. While a linear pattern of LP can be seen due to the koebner phenomenon, linear LP streaks tend to be longer and wider than lesions due to koebnerization. While linear LP represents a rarely recognized subtype of LP, a relationship with the whorled pattern described by Blaschko is rarer still. Psoriasis, lichen striatus, and vitiligo are other acquired conditions that may occur within the lines of Blaschko.

The cause of the linear and whorled pattern described by Blaschko is not known. It has been speculated that these patterns represent embryologic developmental pathways along which some cutaneous cells migrate or proliferate. Mutations that occur in these cell lines prior to their proliferation would lead to a population of abnormal cells. The concept of genetic mosaicism has led to the hypothesis that the juxtaposition of normal and abnormal cell lines can lead to the blaschkolinear phenotype seen in certain genodermatoses. Some of the disorders this hypothesis may help to explain include incontinentia pigmenti, Goltz syndrome, and Happle syndrome. It is possible that an acquired blaschkolinear dermatosis could result from mosaicism for a gene mutation that requires an environmental or immunological trigger for expression to occur.

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Case # 9

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Michael D. Tharp, M.D., Mark D. Hoffman M.D., and Rachel Altman, M.D.

History: This 2-½ year old Hispanic boy with a past medical history of Down's syndrome and transient myelodysplasia of infancy (diagnosed 10/02) recently (2/04) progressing to acute myeloid leukemia presented with a 2 month history of a widespread pruritic skin eruption. The eruption began on his trunk and then spread peripherally, and persisted despite a 3-4 week course of acyclovir (for presumed varicella infection despite negative viral cultures). During this time, the patient remained afebrile without changes in his appetite or energy level.

Physical Findings: Disseminated 2-3 mm pink papules (most with hemorrhagic crust) some coalescing into plaques. Of note, there were a few early pinpoint vesicles on erythematous wheals. No burrows were present and palms/soles were clear of lesions. Later lesions progressed into hemorrhagic vesicles, some umbilicated with crusting.

Laboratory Data:

3/17/04 - WBC 7.19, Hgb 12.6, Hct 37.1, Platelet 5,000
4/6/04 – WBC 9.42, Hgb 6.0, Hct 17.6, Plt 7,000, 9% Seg, 1% Band, 2% Myelo, 2% Pro, 60% Lymph, 2% Mono, 13% Baso, 11% Blasts
Tzank Smear and Viral culture (3/3/04 and 3/11/04) – No neoplastic or viral inclusions identified. No multinucleated giant cells, no herpes simplex virus or varicella zoster virus detected;
(3/5/04)Varicella IgG detected (not IgM) in blood. No herpes simplex IgG or IgM detected.
Blood cultures (3/5/04)– no growth
Aerobic culture of biopsy (3/11/04) – no growth
3/11/04 & 3/3/04 – Electrolytes, Glucose, BUN/ Creatinine, liver function tests within normal limits

Biopsy Description: 3/4/04 Back – Subcorneal pustule. No viral changes are identified.

3/11/04 Back – Subcorneal pustule. Epidermis is acanthotic with overlying central area of serum crust containing numerous neutrophils. Papillary dermis is mildly edematous containing extravasated red blood cells along with a superficial perivascular infiltrate, consisting of lymphocytes, neutrophils and rare eosinophils. Epidermal spongiosis is present.

3/11/04 Back Direct Immunofluorescence – Negative IgG, IgM, IgA, C3; Fibrinogen revealed diffuse dermal staining

Diagnosis: **Atypical Sweet's Syndrome** (Acute febrile neutrophilic dermatosis)

Present Course and Therapy: A diagnosis of atypical Sweet's syndrome in the setting of AML is most consistent clinically and histopathologically. The patient was started on Prednisone at 0.5 mg/kg/day, 1% hydrocortisone ointment for his face, and 0.1% Triamcinolone ointment for his body with significant clearing in several days. Attempts to taper his prednisone resulted in recurrences. Patient has required an additional hospital admission secondary to anemia and thrombocytopenia requiring blood and platelet transfusions.

Discussion: Infants with Down's syndrome are at an increased risk of developing hematologic abnormalities including leukemoid reactions (secondary to infections, hemolysis, or perinatal steroid administration), transient myeloproliferative disorders, and congenital leukemia. There have been numerous reports of vesiculopustular eruptions in patients with Down's syndrome and myeloproliferative disorders. The differential diagnosis for vesiculopustular dermatosis in an infant with Down's includes a transient myeloproliferative disorder as opposed to chronic, congenital leukemias requiring therapy. The eruption associated with transient myeloproliferative disorder displays pathergy, classically is concentrated on the face with subsequent spread to the trunk, and immature neutrophils are seen on histopathology. Although most cases of transient myeloproliferative disorder have a sustained, spontaneous remission, approximately 20% of patients may ultimately develop acute leukemia later in life. Unfortunately, there are no well-established prognostic features that may help to predict which infants will later develop leukemia.

Sweet's syndrome/acute febrile neutrophilic dermatosis is characterized by fever, neutrophilia, and erythematous, red/purple papules, nodules, and plaques (less commonly bullae, pustules or ulcers) which occur most frequently on the upper body/face. The exact etiology is unknown but is thought to be a hypersensitivity reaction leading to cytokine production with subsequent neutrophil activation and infiltration. Classical Sweet's may be associated with infection (gastrointestinal tract or upper respiratory tract), pregnancy, post-vaccination, or inflammatory bowel disease. Malignancy associated Sweet's is most commonly associated with hematologic (acute myelogenous leukemia most commonly) disorders. Skin lesions may be more diffuse in malignancy associated Sweet's.

Laboratory findings usually reveal an elevated sedimentation rate and peripheral leukocytosis with predominant neutrophilia. However, in malignancy associated Sweet's, anemia, abnormal platelet count and a normal or low neutrophil count may be observed. Pathology reveals edema of the papillary dermis and dermal papillae with a dense and diffuse infiltrate of mature neutrophils in the superficial dermis, occasionally admixed with lymphocytes, eosinophils or histiocytes. On occasion, the neutrophils may migrate into the overlying epidermis or underlying subcutaneous adipose tissue (the specific location of the neutrophils determines the clinical appearance of spongiotic vesicles or subcorneal pustules).

Treatment of choice is systemic corticosteroids at 0.5 mg/kg/day – 1 mg/kg/day (lesions and symptoms promptly resolve in either classical or malignancy associated Sweet's) with gradual tapering. Localized Sweet's may be treated with high-potency topical corticosteroids or intralesional corticosteroids. Potassium iodide and colchicines are other first line agents. Other reported successful agents include indomethacin, clofazamine, cyclosporin, or dapsone.

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Case # 10

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Mark D. Hoffman M.D., Arthur R. Rhodes M.D. and Alix J. Charles, M.D.

History: This 62 year old African American woman presented with a six week history of painful red brown nodules on the legs bilaterally. The lesions did not drain. The patient denied nausea or abdominal pain. Six months prior, while being worked up for abdominal pain, the patient was found to have liver metastasis that proved to be neuroendocrine in origin. A primary neuroendocrine tumor could not be identified on abdominal CT scan. An incisional biopsy of one of her leg lesions was performed and tissue was submitted for cultures and histopathologic examination. Two weeks after biopsy, the patient was admitted to the hospital.

Past Medical History: Metastatic ductal breast carcinoma in 1996, treated with surgery and chemotherapy. PMH is otherwise unremarkable.

Physical Findings: Discrete 2 to 10 cm red-brown nodules are scattered over the lower legs bilaterally. Some nodules display a hemmorhagic crust. The lesions are tender to palpation.

Laboratory Data: At Presentation: Cr 7.9 Ca 8.5 Alk.Phos. 180 SGOT 32 SGPT 21 Amylase 124
Upon Admission: Cr 14.2 Ca 7.4 Alk.Phos. 146 SGOT 21 SGPT 14 Amylase 85 Lipase 7159

Biopsy Description: A mixed cell infiltrate composed of neutrophils, lymphocytes, histiocytes, and giant cells is present at the dermal-subcutaneous junction. The infiltrate involves both septa and fat lobules. Multiple foci of fat necrosis are present. Tissue stains and cultures for bacteria, fungi, and acid fast bacilli were negative.

Diagnosis: **Pancreatic Panniculitis** (Subcutaneous Fat Necrosis in Pancreatic Disease)

Present Course and Therapy: Two weeks after her incisional biopsy, the patient was admitted to the hospital for anemia, azotemia, and an acutely elevated creatinine. Despite rapid deterioration in her mental status and renal function, the patient did not wish to be dialyzed and expired one week after admission. Her family declined an autopsy.

Discussion: Pancreatic panniculitis, or disseminated fat necrosis, is a rare complication of several pancreatic diseases. It is seen in up to 3% of patients with pancreatic disease, and is associated with a high degree of morbidity and mortality. Males are affected more often than females, and the incidence is higher in the fourth through sixth decades. The majority of cases occur in association with acute or chronic pancreatitis, but it has also been seen with

pancreatic carcinoma (especially acinar cell type). In some patients no demonstrable pancreatic disease is found although elevated serum levels of pancreatic enzymes are noted. Clinically, cutaneous lesions appear as tender, erythematous to brown subcutaneous nodules that may spontaneously ulcerate and exude an oily or hemmorhagic material. The lower extremities near the ankles or the knees are a frequent site of lesions, although the thighs, buttocks, arms, and abdomen can also become involved. Up to 50% of patients can also develop arthritic symptoms. These clinical signs are the result of liquefactive necrosis of subcutaneous fat and periarticular tissue. The histologic findings are characteristic and consist of a mostly lobular panniculitis with intense coagulative necrosis of adipocyte. This leads to "ghost cells" which are anucleate adipocytes with a granular and basophilic cytoplasm. Dystrophic calcification may also be seen.

Although the precise mechanism of pancreatic panniculitis is unknown, it is thought to be caused by leakage of serum lipase into the subcutis. This theory has been supported by findings of pancreatic lipase in areas of fat necrosis as well as anti-lipase antibodies within necrotic adipocytes. Treatment of this condition is supportive, although a somatostatin analog has been shown to favorably alter the course of pancreatitis in animal models.

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Case # 11

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Mark D. Hoffman, M.D., Arthur R. Rhodes, M.D. and Darrell W. Gonzales, M.D.

History: This 63 year old white male presented to the emergency department with a one week history of intermittent fevers, headaches, malaise, and the new onset of painful lesions on his face, neck, and forearms. He was admitted to the hospital for hypotension and evaluation of possible septicemia. Despite broad spectrum antibiotics the patient continued to develop intermittent fevers with an increase in the size and number of lesions.

Past Medical History: The patient's past medical history was significant for myelodysplastic syndrome, hypertension, and nonischemic cardiomyopathy. His medications included digoxin, sotalol, furosemide, coumadin, and lisinopril.

Physical Findings: On physical examination, the patient demonstrated erythematous well-demarcated plaques on his ears, chin, and neck. The dorsal aspect of his forearms and hands demonstrated multiple tender hemorrhagic bullae bilaterally. His conjunctivae were noted to be injected. There were no oral lesions noted. There was no cervical, supraclavicular, axillary, or inguinal adenopathy.

Laboratory Data: WBC: 23,100 (4,000-10,000), Hgb: 7.6 (13.5-17.5), HcT: 22.9% (41-53), PLT: 177,000
Seg%: 93, Lymph%: 3, Mono%: 0, Baso%: 0, Blasts%: 2
Prot: 5.5 (6.0-8.2), Alb: 1.8 (3.5-5.0), CA: 7.3 (8.7-10.7), Tbil: 0.1 (0.2-1.3), AP: 254 (30-125), SGOT 19 (5-55), SGPT: 31 (31-50)
Tissue cultures for bacteria and fungi were negative.
Blood cultures negative.
Chest X-ray: normal

Biopsy Description: An initial punch biopsy from the patient's right arm demonstrated a well-defined neutrophilic infiltrate within the epidermis and papillary dermis. There was no evidence of vasculitis or thrombi in the blood vessels. PAS and gram stains were negative for organisms. The well- circumscribed nature of the neutrophilic infiltrate was not felt to be consistent with a diagnosis of Sweet's syndrome.
A repeat biopsy from the patient's right forearm demonstrated a small focus of neutrophilic infiltrate in the superficial dermis compatible with a diagnosis of Sweet's syndrome.

Diagnosis: **Bullous Sweet's Syndrome** (Acute febrile neutrophilic dermatosis)

Present Course and Therapy: During the patient's hospitalization, he was started on prednisone 60 mg per day. Within twenty four hours his fever ceased. Over the next week, there were no new plaques or bullae, and his older lesions rapidly crusted. Following discharge from the hospital and over the next several weeks, his dermatosis resolved with minimal residual hyperpigmentation. His prednisone was gradually tapered over 4 months, with no recurrence of fever or lesions. Unfortunately, the patient's blast count began to increase. After four months from his initial diagnosis of Sweet's syndrome, he developed acute myelogenous leukemia died shortly thereafter despite aggressive chemotherapy.

Discussion: Sweet's Syndrome was originally described by Dr. Robert Douglas Sweet in 1964. The Syndrome is characterized by fever, neutrophilia, painful red papules, nodules, and plaques, and an infiltrate consisting predominantly of mature neutrophils diffusely distributed in the upper dermis. It has a worldwide distribution and no racial predilection.. Women between the age of 30 and 50 years are individuals in whom classical Sweet's syndrome most commonly occurs. It has, however, been documented in men, younger adults and children.

Sweet's syndrome presents in three settings. Classic or idiopathic Sweet's syndrome (up to 71%) may be associated with infection (upper respiratory tract or gastrointestinal tract), inflammatory bowel disease (Crohn's disease and ulcerative colitis), or pregnancy (2%). In up to 20% of patients, Sweet's syndrome represents a paraneoplastic process in which either the onset or recurrence of the dermatosis is temporally associated with the presence of underlying malignancy. Acute myelogenous leukemia is the most common malignancy associated with paraneoplastic Sweet's Syndrome. Myelodysplastic syndrome and solid tumors (genitourinary, breast, and gastrointestinal cancers) have also been reported. In the majority of cases, the skin lesions appear concurrently with the discovery of malignancy or precede the diagnosis of leukemia by up to several months or even years. Drug-induced Sweet's syndrome most frequently occurs in patients who are receiving granulocyte-colony stimulating factor (G-CSF), but has also been documented in patients receiving antibiotics (minocycline, nitrofurantoin, or trimethoprim-sulfamethoxazole), antiepileptics, antihypertensives, oral contraceptives, and All-*trans* retinoic acid.

Sweet's syndrome patients may appear dramatically ill. Fever and leukocytosis usually accompany the skin eruption. Other symptoms may include arthalgia, general malaise, headache, and myalgia. The skin lesions typically appear as tender, red or purple-red, well-demarcated papules or nodules that may coalesce to form irregular, sharply demarcated plaques. Cutaneous pathergy is frequently present. Lesions occur most often on the face, upper extremities, and neck. The plaque may have a transparent appearance related to the pronounced edema in the upper dermis. Although more rare, frankly pustular, bullous, or ulcerative lesions have been documented and are usually associated with underlying malignancy. Oral and eye involvement (conjunctivitis or episcleritis) have been reported. Alveolitis, sterile osteomeyelitis, renal, hepatic, and central nervous system involvement may occur. The most consistent laboratory findings include an elevated erythrocyte sedimentation rate and peripheral leukocytosis with neutrophilia. In patients with malignancy-associated Sweet's syndrome, there may be anemia, a normal or low neutrophil count, and abnormal platelet count. Proteinuria, and less often hematuria, may be present in patients with renal involvement. Hepatic enzyme abnormalities have been observed in patients with liver involvement.

The pathologic features of Sweet's characteristically involve the dermis. In addition to edema of the dermal papillae and papillary dermis, there is a dense infiltrate of mature

neutrophils in the superficial dermis. Swelling of the endothelial cells, dilatation of the small blood vessels, and fragmentation of the neutrophil nuclei are frequently present. Neither fibrin deposition nor neutrophils are present within the vessel wall. The histologic differential diagnosis includes other neutorphilic dermatosis including bowel-bypass-related dermatosis, erythema elevatum diutinum, granuloma faciale, halogenoderma, leukocytoclastic vasculitis, neutrophillic eccrine hidradenitis, pyoderma gangrenosum, and rheumatoid neutrophilic dermatitis.

Diagnostic criteria for idiopathic, malignancy-associated, and drug-induced Sweet's syndrome, have been established. For idiopathic and malignancy associated Sweet's syndrome, criteria include (1) abrupt onset of painful erythematous plaques/nodules; (2) histopathologic evidence of a dense neutrophilic infiltrate without evidence of leukocytoclastic vasculitis; (3) fever > 38 degrees Celsius, (4) Associated underlying malignancy, inflammatory disease, pregnancy or preceded by upper respiratory or gastrointestinal infection; (5) excellent response to treatment with systemic glucocorticoids or potassium iodide; and (6) abnormal laboratory findings at presentation (e.g. ESR > 20 mm/hr, neutrophils > 70 percent). Numbers 1 and 2 must be present and two of criteria 3-6 for a diagnosis of Sweet's syndrome.

The etiology of Sweet's syndrome is unknown, but is presumed to be a hypersensitivity reaction which leads to stimulation of a cascade of cytokines that precipitate neutrophil activation and infiltration.

Without treatment, the lesions of Sweet's syndrome may persist for weeks or even several months. Lesions may then involute without scars. In some patients with solid tumor-associated Sweet's syndrome, resolution of symptoms and lesions occurred following complete resection of the tumor. In patients with drug induced Sweet's syndrome, discontinuation of the associated agent was often followed by relief of symptoms and clearing of lesions. Systemic corticosteroids have been the treatment of choice in most large series of patients reported. Prednisone is used with an initial dose of 0.5-1.0 mg per kg per day. A rapid response is usually seen taking one to several weeks. Unfortunately, recurrence is common and is seen in about 15%. Other treatment modalities include topical and intralesional corticosteroids, either as adjunctive treatment or solo therapy. Indomethacin and potassium iodide have also been reported to be successful. Case reports of cyclosporine, doxycycline, dapsone, colchicine, and clofazamine have been cited as alternative treatments for recalcitrant cases.

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Case # 12

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Mark D. Hoffman, M.D. and Darrell W. Gonzales, M.D.

History: This 51 year old A.A. female presented with a three month history of painful and pruritic lesions on her palms. She denied prior history of such lesions. New papules were reported to develop weekly with older lesions remaining fixed and stable in size. Although here fingers were reported to be painful with cold exposure, she denied any associated color changes. Her review of symptoms was otherwise normal. She had recently been prescribed cyclosporine for presumed palmar calcinosis cutis secondary to CREST syndrome with no improvement in her condition.

Past Medical History: The patient had a history of primary biliary cirrhosis diagnosed five years prior and was awaiting a liver transplant. Her medications included ursodial, mycophenolate mofetil, prednisone, cyclosporine, and lansoprazole.

Physical Findings: The patient's palms and ventral fingertips were notable for 1 to 3 mm soft yellow-colored papules with some having a mild erythematous base. Her palmar creases were notable for yellow plaques with extension beyond the creases. Her sclera was noted to be icteric. There was no evidence of similar lesions in her mouth or around her eyes, elbows, antecubital fossa, or finger web spaces. Her chest, back, and abdomen were clear. There was no evidence of periungual telangiectasias or sclerodactly.

Laboratory Data: The following laboratory results were abnormal or positive: Cholesterol 1532 mg/dl (0-200), HDL 22 mg/dl (35-80), TRIG 484 mg/dl (30-135), LDH 659, GGT 4058 (14-51), SGOT 149 U/L (5-55), SGPT 86 (3-50), Anti-mitochondrial antibody >1:1280 (<1:20). A CT guided biopsy of the patient's liver demonstrated fibrosis of the portal areas, scattered granulomas, and pericentral liver damage. The following were negative or within normal limits: CBC, WBC and differential, BUN, Creatinine, glucose, ANA, anti-RNP, Anti-SM, Anti-SCL 70, RPR, TSH, Hep A, Hep B, Hep C, Hep D, Hep E.

Pathology Description: The epidermis exhibited a thick stratum corneum overlying a mildly irregular acanthotic epidermis. The dermis revealed an infiltrate that spanned from the papillary dermis to the mid-dermis consisting of foam cells with few lymphocytes and histiocytes. Multinucleate giant cells were also seen within the infiltrate.

Diagnosis: **Plane Xanthoma**

Present Course and Therapy: Shortly after the biopsy confirmation of palmar xanthoma, the patient underwent a successful liver transplant. The yellow papules and plaques on her hand resolved within several weeks of her surgery and she continues to do well.

Discussion: Primary Biliary Cirrhosis (PBC) is a chronic progressive cholestatic liver disease of unknown etiology that usually affects middle-aged women and eventually leads to liver failure and need for liver transplantation. PBC is characterized by destruction of small intrahepatic bile ducts, portal inflammation, and progressive scarring. The estimated incidence is 3.9 to 15 cases per million population per year. There is an association between PBC and other diseases considered to have an autoimmune basis. Up to 84% of patients with PBC may have thyroiditis, scleroderma, rheumatoid arthritis, or Sjogren's Syndrome. The frequency of the association between CREST syndrome and PBC ranges from 3-17%. Out of the many circulating autoantibodies, the most important diagnostically and perhaps pathogenetically is anti-mitochondrial antibody (AMA) AMA are found in 95% of patients with PBC and they have a specificity of 98% for this disease. Their role in the pathogenesis of this disorder is unclear and the titers do not correlate with the severity or rate of progression of disease.

Fatigue and pruritus are the usual presenting symptoms. Physical exam findings are variable and may include hepatosplenomegaly, jaundice, and hyperpigmentation in a butterfly distribution on the back resulting from the patient having difficulty in reaching that area. The diagnosis is based on the clinical picture and associated elevation of the alkaline phosphatase level, the presence of anti-mitochondrial antibody in the serum, and liver histopathological findings. PBC progresses in most cases but the rate of progression varies greatly among individuals. Treating asymptomatic patients is controversial and liver transplantation is the only treatment that clearly improves the natural history of PBC. The median survival of asymptomatic patients is 10-16 years and that for symptomatic patients is 7 years.

Cutaneous xanthomas develop as a result of intracellular and dermal deposition of lipid. One of the major distinguishing clinical features of xanthomatous tissue is a characteristic yellow to orange hue. Lesions may present with a number of morphologies, including macules, papules, plaques, and nodules. The morphology and anatomic location of the lesions can suggest the type of underlying lipid disorder. Xanthomas can exist in the setting of primary or secondary disorders of lipid metabolism. Early recognition of these lesions can make a significant impact on the diagnosis, management, and prognosis of patients who suffer from an underlying disease.

Plane xanthomas are seen as yellow to orange, non-inflammatory macules and plaques. They can be circumscribed or diffuse. Their location can vary and the site often serves as a clue to the particular underlying disease state. For example, intertriginous plane xanthomas may occur in the antecubital fossae or the web spaces of the fingers where they are almost pathognomonic for homozygous familial hypercholesterolemia. Plane xanthomas of the palmar crease, or xanthoma striatum palmare, are almost diagnostic for dysbetalipoproteinemia, especially when accompanied by tuberous xanthomas.

Plane xanthomas of the hands and feet are characteristic of disorders that cause hepatic cholestasis, such as primary biliary cirrhosis and biliary atresia. On the palms, they can be differentiated from xanthoma striatum palmare by their plaque appearance, extension beyond the creases, and evolution in a grayish or dusky hue. In these conditions, free cholesterol cannot be excreted properly into bile and is instead regurgitated into plasma, where free cholesterol binds with albumin and phospholipid to form an abnormal lipoprotien called lipoprotein X. Infiltration of lipoprotein X or its components into dermis and subcutaneous tissue is probably

responsible for the development of the planar xanthomas. Correction or improvement of the hepatic obstruction results in lowering of plasma cholesterol and resolution of the xanthomas. Plasma exchange has been one effective means of temporarily correcting hypercholesteremia in primary biliary cirrhosis. Liver transplantation is the only treatment that clearly improves the natural history of primary biliary cirrhosis.

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Case # 13

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: John Kalis, M.D. and Darrell W. Gonzales, M.D.

History: The patient is a 35 year-old male presenting with a 3 year history of telangiectasias on his lips and tongue. Despite treatment with laser therapy two years ago he has continued to develop new lesions. In addition to his telangiectasias, the patient reports a 10 year history of daily nosebleeds requiring frequent visits to the emergency department. He denies any history of migraines, seizures, transient ischemic attacks, melana, or dyspnea on exertion.

Past Medical History: No significant past medical history.

Social and Family History: The patient has one 10 month old healthy son. He reports that his mother has had similar telangiectasias on her tongue, lips, and hands since her fifth decade. Additionally, the mother has had episodes of epistaxis which also developed during her fifth decade. There is no family history of congestive heart failure, strokes, or intracerebral bleeding. The patient is a police officer with no difficulty performing the physical requirements of his job.

Physical Findings: On physical exam the patient was found to have multiple telangiectasias on his tongue and the vermillion border of his lips. There was no evidence of hepatosplenomegally or an abdominal bruit. His fingernails lacked evidence of clubbing.

Laboratory Data: A WBC and chest X-ray were normal. The patient recently underwent an endoscopy and colonoscopy with only several colonic polyps identified and no evidence of telangiectasias.

Diagnosis: **Hereditary Hemorrhagic Telangiectasia** (Osler-Weber-Rendu Syndrome)

Discussion: Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu, is an autosomal dominant disorder that leads to mucocutaneous and visceral fibrovascular dysplasia. Progressive development of arteriovenous malformations and telangiectasias occurs, predominantly involving the skin, mucosa, viscera, lungs, and brain.

Hereditary hemorrhagic telangiectasia is inherited in an autosomal-dominant manner and occurs in all races with equal gender distribution. There is considerable variability of expression and severity between and even among family members. Given its tremendous heterogeneity, HHT has long been viewed as a rare condition. Recent evidence, however, indicates that this disorder may in fact be more frequent than previously thought. A prevalence ranging between 1 in 2,351 individuals in a region in France has been identified and 1 in 16,5000 individuals in Vermont. Penetrance is high with an age-dependent phenotype that is nearly complete by the age of 40 to 45 years. The homozygous state appears to be lethal.

Genetic linkage studies have provided insights into the causes of HHT. Mutations in at least two genes are associated with HHT in different families. Endoglin (ENG) on chromosome 9 and activin-like kinase receptor 1 (ALK-1) on chromosome 12 have been identified as the genes responsible for two variants of HHT, HHT1 and HHT2, respectively. HHT1 families have a higher prevalence of pulmonary AVMs than HHT2 families, who generally have a milder phenotype and later onset. ENG and ALK-1 encode a homodimeric integral membrane glycoprotein. The molecule is expressed mainly on vascular endothelial cells and is the surface receptor for the transforming growth factor ß (TGF-ß) superfamily, which mediates vascular development and remodeling through effects on extracellular matrix production.

In HHT, the malformation consists of aberrant vascular development with multiple dilated vessels that are lined by a single layer of endothelium that is attached to a continuous basement membrane. The dilated and convoluted vessels have excessive layers of smooth muscle without elastic fibers. Various explanations for the characteristic bleeding of these vessels include insufficient smooth muscle contractile elements, endothelial cell junction defects, perivascular connective tissue weakness, and endothelial cell degeneration. No single pathognomonic histologic characteristic for telangiectasias in HHT exists.

Hereditary hemorrhagic telangiectasia is progressive over time. The most common presentation is varying degrees of recurrent spontaneous epistaxis (up to 90%). Recurrent epistaxis begins by the age of 10 years in many patients and by the age of 21 in most, becoming more severe in later decades in about two thirds of affected persons. It may be so severe as to require multiple transfusions and oral iron supplementation. Later in life, usually by the third or fourth decade, mucous membrane hemorrhage involving the gastrointestinal tract develops (20%). The characteristic lesions, cutaneous macular telangiectasias, seldom develop before the second or third decade of life, but affect about 70% of patients.

Pulmonary AVMs affect up to 20% of patients with HHT. The right-to-left shunt leads to cyanosis, hypoxemia, exertional dyspnea, clubbing, and embolic events. Often multiple, they have a predilection for the lower lobes with symptoms developing in 50% by the third or fourth decade. Neurologic symptoms may occur (4-11%) and include migraine, brain abscesses (from embolic events), transient ischemic attacks, stroke, seizure, and hemorrhage. Upper and lower gastrointestinal tract hemorrhage occurs in many, but usually do not develop until the fifth or sixth decade of life. Liver involvement may occur in up to 30% leading to high-output congestive heart failure, portal hypertension, hepatic encephalopathy, and liver failure.

The Scientific Advisory Board of the HHT Foundation has developed the Curacao criteria for the diagnosis of hereditary hemorrhagic telangiectasia. This includes spontaneous and recurrent epistaxis, multiple telangiectasias at characteristic sites (lips, oral cavity, fingers, nose), visceral AVM (pulmonary, cerebral, hepatic, spinal) or gastrointestinal telangiectasias, or a first degree relative with HHT. Patients are considered to have a definite diagnosis when three or more of the criteria are met and possible when two of the criteria are met. Diagnostic laboratory-based genetic testing is currently available only on a limited basis.

The management of patients with HHT includes treatment of identified complications such as nosebleeds, GI bleeding, anemia, and AVMs, as well as surveillance for undiagnosed AVMs. The HHT Foundation recommends all patients having a brain MRI with and without gadolinium to screen for cerebral AVMs. Cerebral AVMs greater than one cm in diameter are treated using neurovascular surgery, embolotherapy, or stereotactic radiosurgery. By age 20, it is recommended that a contrast echocardiography (echo bubble) be performed to screen for pulmonary AVM. Evidence of pulmonary AVM should be followed with a CT to determine if AVMs indicate treatment with embolization . (>3mm) and repeated every five years for possible growth. There is currently no agreement on screening for AVM in the first

decade of life, but a finger oximetry every 1-2 years in affected or children at risk may be advisable. Treatment for cardiac failure or liver failure secondary to hepatic AVM is problematic with embolization proving lethal secondary to hepatic infarctions in some patients. Liver transplantation is currently considered the treatment of choice for those whose symptoms necessitate treatment.

If possible, anti-coagulants such as aspirin and non-steroidal anti-inflammatory agents that interfere with normal clotting should be avoided. To prevent brain abscess, antibiotic prophylaxis is recommended for dental and surgical procedures in patients with pulmonary AVM or family history of pulmonary AVM until such a malformation is ruled out. Because genetic testing is currently not widely available, screening of relatives for the presence of cutaneous telangiectasias as well as pulmonary AVMs and cerebral vascular malformations may useful.

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Case # 14

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Michael D. Tharp, M.D. and Kelle L. Berggren, M.D.

History: This 64 year old man was referred by Dr. Marianne O'Donoghue to Rush with a generalized erythematous and petechial eruption of 10 years duration. The eruption tended to change location from week to week but was usually seen involving the arms, flanks, back and legs. The patient complained of pruritus but not pain. He felt well and had a negative review of systems. A biopsy was obtained (see below) and the patient was treated with numerous topical corticosteroids, Protopic ointment, antihistamines, UVB and PUVA with only moderate response. A trial of aspirin or NSAID elimination as well as changing all of his anti-hypertensive meds provided no relief of the eruption.

Past Medical History: The patient has a history of hypertension treated with clonidine, cardizem, lasix and K-Dur. He also has a history of asthma treated with an albuterol inhaler as needed. He had multiple blood transfusions as a child.

Physical Findings: An erythematous, mildly scaling eruption with petechiae was noted on his arms, legs and trunk. No lymphadenopathy or hepatosplenomegaly was noted.

Laboratory Data:

T-Cell gene rearrangement indeterminate
SPEP normal except the α-2 region decreased slightly
PT/PTT normal
Hemoglobin 15.9
Platelets 189,000
Wbc 6,700

HIV Ab negative
Hep B and C Ab negative
SGOT 37 (nl)
SGPT 68 (sl. High)
Creatinine 1.2

Biopsy Description:

8/30/01: Abdomen and left arm - Spongiotic dermatitis with focal exocytosis of lymphocytes and superificial perivascular lymphocytic infiltrate.
12/31/01: Right posterior axilla – Interface dermatitis, vacuolar type with lymphocytes and extravasated erythrocytes around several blood vessels.
12/21/01: Left abdomen – Interface dermatitis, lichenoid type with extravasated erythrocytes within the papillary dermis and exocytosis of lymphocytes.
6/13/02: Left arm and left flank – Spongiotic and lichenoid dermatitis, lymphocytic type with extravasated red blood cells.

Diagnosis: **Generalized Schamberg's Disease** (treated with Rutin)

Present Course and Therapy: Based on the resistance to multiple treatment regimens, a trial of Rutin, an oral bioflavonoid, at 50 mg BID and ascorbic acid 500 mg BID was initiated. The eruption almost completely cleared within 4 weeks and has remained well controlled with continuing therapy.

Discussion: Progressive pigmented purpura (PPP) can be clinically divided into 4 main subtypes: progressive pigmentary dermatosis of Schamberg, purpura annularis telangiectodes of Majocchi, pigmented purpuric lichenoid dermatitis of Gougerot and Blum and eczematoid-like purpura of Coucas and Kapetanakis. Schamberg's Disease is characterized by orange-brown patches of the skin and reddish "cayenne pepper" spots, appearing within and at the edge of older lesions. The lower extremities is the usual site; however, lesions can occur elsewhere. The course of the disease is chronic with lesions clearing while new areas develop. Histologic exam shows a mild perivascular lymphocytic infiltrate, extravasated erythrocytes and macrophages containing hemosiderin deposits. The dermal infiltrate consists primarily of CD4+ lymphocytes and CD1a+ dendritic cells. Strong expression of ICAM-1 (intercellular adhesion molecule 1), LFA 1 (leukocyte function antigen 1) and ELAM 1 (endothelial leukocyte adhesion molecule 1) by cells of several lineages is observed, suggesting that these adhesion molecules play a key role in regulating leukocyte traffic into tissues and in regulating lymphocyte-dendritic cell interaction. Cytokines released by infiltrating leukocytes (especially TNF-α) stimulate the expression of ELAM-1 by endothelial cells and cause defective release of plasminogen activator which contributes to the perivascular deposits of fibrin. It has also been postulated that reactive oxygen species induce capillary permeability in PPP. In a few studies, the infiltrate (specifically CD4, CD1a and the CAMs) disappeared in all patients after treatment with local corticosteroid and PUVA treatment.

Although chronic PPP represents a benign condition, patients are often distressed by cosmesis. The disease, however, is often resistant to many forms of therapy. Treatment regimens with topical/oral corticosteroids, PUVA, cyclosporine, petoxyfylline, griseofulvin and colchicine have shown limited success. Because a role for reactive oxygen species has been suggested in PPP, bioflavonoids, which induce increased capillary resistance and inhibit pro-inflammatory enzymes, have been proposed as potential therapeutic agents. Furthermore, bioflavonoids and ascorbic acid have potent anti-oxidative radical scavenging activities and their protective effects may be additive. As a result, these agents in combination may exert angioprotective and anti-inflammatory properties in vivo that lead to improvement in capillaritis in PPP.

Flavonoids are naturally occurring polyphenolic compunds that are ubiquitous in photosensitizing cells. The main dietary sources are fruits and vegetables. Consumption has been linked to protection against heart disease and cancers, and improved signs and symptoms of chronic venous insufficiency, hemorrhoids and diabetic retinopathy.

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Case # 15

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Lady Christine C. Dy, M.D. and Kelle L. Berggren, M.D.

History: This 39 year old woman presented to our dermatology clinic with a 15 year history of red papules on her left thigh. In the previous six months, the red papules increased in number and had progressed to involve her right thigh, back, chest and forehead. There is no associated pain or pruritus. She denies acroparesthesias or hypohidrosis.

Past Medical History: The patient has a history of "easy bruising". After childbirth, she had to have a partial hysterectomy secondary to prolonged bleeding. Breast implants were complicated by rupture and continuing pain. Recently, the patient "fainted" for unknown reasons and was seen by neurology.

Medications: None

Physical Findings: Hundreds of 1-3 mm smooth, red papules are seen on her thighs, back, chest and forehead. There is a marked predominance of lesions on her left side.

Laboratory Data:

PT - 12.9 (10.8-12.8)	Liver Function Tests Normal
PTT – 27	Hemoglobin – 14.1
BUN/Cr Normal	Platelets – 243
	Urinalysis Normal

Biopsy Description: A biopsy done on her left thigh was consistent with a cherry angioma.

Diagnosis: **Eruptive Cherry Angiomas** (presenting in Blaschko's lines)

Present Course and Therapy: The patient was referred to gastroenterology for a colonoscopy and to ophthalmology for a slit lamp exam to check for corneal opacities associated with Fabry's Disease. A MRI/MRA ordered by neurology showed no evidence of vascular malformation. A few of the angiomas have been treated with pulsed dye laser for cosmetic reasons.

Discussion: Cherry angiomas, also knows as Campbell de Morgan spots or senile angiomas, are the most common cutaneous vascular proliferation. Despite their frequency, the sudden appearance of multiple cherry angiomas, an occurrence also known as eruptive angiomatosis, has been rarely reported and its etiopathogenesis is unknown. In his original description, Campbell de Morgan expressed suspicion that such spots were a sign of occult malignancy. There have been large scale studies to refute this claim and it is now the accepted view that there is no association between these lesions and malignancy. However, eruptive cherry angiomas have been associated with POEMS syndrome

(polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes), Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, plasmacytosis, cerebral cavernous malformations, solid organ transplantation, chronic graft-versus-host disease, cyclosporine therapy, sulfur mustard gas, 2-butoxyethanol (glycol ether solvent), prolonged exposure to bromides and argon laser therapy. It is interesting to note that eruptive cherry angiomas might represent a nonspecific response either to inhalation of noxious agents or proliferating plasmacytes producing angiogenic cytokines. However, the generally accepted view is that these lesions develop in most people as they age (usually start between 30 and 50 years old) and it would be impossible to associate their development with anything. Traditionally, electrosurgery (hyfercator) has been used to treat cherry angiomas and more recently lasers have been utilized. A recent study showed that the KTP laser and the hyfercator were able to clear angiomas but the KTP laser was superior as fewer treatment episodes were required and there were fewer side effects.

Fabry's Disease, an inborn error of glycosphingolipid metabolism, must be considered in the differential diagnosis of eruptive cherry angiomas. The enzymatic defect in α-galactosidase A is transmitted in an X-linked recessive fashion. Clinically, males have the characteristic skin lesion of angiokeratoma corporis diffusum as well as acroparesthesias, corneal and lenticular opacities, hypohidrosis, and cardiac and renal dysfunction. The clinical course and prognosis of affected males and heterozygous females differ significantly. Approximately 30% of heterozygotes have a few isolated skin lesions, fewer than 10% have acroparesthesias and about 70% have the whorllike corneal dystrophy. Renal findings include hyposthenuria; the occurrence of erythrocytes, leukocytes, and granular and hyaline casts in the urinary sediment. A few heterozygotes have been described with disease as severe as that observed in classically affected males.

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Case # 16

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Arthur R. Rhodes, M.D. and Rachel S. Altman, M.D.

History: This 20 year old white male presented with a 3 week history of a rash, abdominal pain, and myalgias. The rash began on his lower extremities, spreading to involve his trunk and upper extremities, and was associated with right-sided intermittent abdominal pain. Despite symptoms, he traveled to Italy where he developed increasing abdominal pain, associated with arthralgias and myalgias prompting an 11 day hospital admission in Italy, during which time he underwent an appendectomy. He signed out of the Italian hospital against medical advice, returned to America and immediately visited our dermatology service.

Past Medical History: Non-contributory

Physical Findings: Bilateral lower and upper extremities, plantar surfaces, buttock and trunk with violaceous purpuric papules and macules.

Laboratory Data:
1/22/04 – urinalysis with 30 mg/dl protein, no glucose, moderate blood, 15 RBC/hpf
AST 62, ALT 91
1/28/04 – Renal ultrasound revealed normal appearing kidneys
2/24/04 – urinalysis with 30 mg/dl protein, glucose 100-250 mg/dl, small blood, 1 RBC/hpf
CRP <1, ESR 3, Complete blood count, metabolic profile, coagulation profile and liver function tests all within normal limits

Biopsy Description: 1/22/04 – Left lateral thigh punch biopsy revealed a superficial perivascular infiltrate composed of lymphocytes and many neutrophils along with focal extravasated red blood cells. Neutrophilic nuclear debris was identified. The vessels were intact without evidence of fibrinoid necrosis.

Diagnosis: **Henoch-Schönlein Purpura**

Present Course and Therapy: The patient was admitted to the medical inservice upon presentation at RUSH and was started on prednisone 60 mg daily. The renal service did not feel that a renal biopsy was necessary. The patient was monitored for 2 days in the hospital prior to discharge. His rash slowly dissipated following admission. Prednisone was successfully tapered. He is currently followed by the renal service and is symptom free.

Discussion: Henoch-Schönlein purpura is a syndrome first described by Heberden in 1801, Schönlein in 1847, and Henoch in 1874. The syndrome is acute and self-limited consisting of leukocytoclastic vasculitis, manifesting as purpura, arthritis, abdominal pain, gastrointestinal bleeding and nephritis. Approximately one third of patients experience recurrences. Long-term prognosis is directly dependent on the severity of renal involvement. The exact etiology is unknown. IgA plays a central role in the immunopathogensis, with clinical

features being a consequence of widespread leukocytoclastic vascuilitis secondary to IgA deposition in vessel walls. HSP is the most common small vessel vasculitis that affects children, its incidence being 10 per 100,000 children per year. HSP affects all ages, with peak incidence from ages 2-5 years old (boys>girls). HSP is often more severe in adults, who suffer increased and prolonged recurrences. Adults may also manifest bullous or necrotic lesions which are unusual in children. HSP is often milder in infants (<2 years old) who demonstrate a low occurrence of renal and abdominal complications. HSP occurs throughout the year, with most cases presenting from fall to spring. The American College of Rheumatology in 1990 proposed criteria for classification of HSP. At least 2/4 of following criteria are required: age <20 years at onset, 2) palpable purpura, 3) bowel angina (diffuse abdominal pain or bowel ischemia, usually with bloody diarrhea), 4) biopsy showing granulocytes in walls of arterioles or venules.

Occurrences have been noted to be preceded by upper respiratory infection. Previously described pathogens include group A beta-hemolytic streptococcus, hepatitis B virus, HIV, adenovirus, mycoplasma, Bartonella henselae, herpes simplex virus, Helicobacter pylori, Toxocara canis, and human parvovirus B19. However, there appears to be no single pathogen or environmental agent which is a proved precipitating cause of HSP. In addition, numerous reports cite induction by various medications including ciprofloxacin, acetyl salicylic acid, vancomycin, carbidopa/ levodopa, cocaine, ACE inhibitors, carbamazepine, and streptokinase.

Histopathologic findings of HSP include leukocytoclastic vasculitis affecting small arterioles and venules with neutrophil infiltration in and around dermal vessels, often with leukocytoclasia. Immunofluorescence reveals IgA deposition in vessel walls, with lesser amounts of C3 and fibrin. Renal biopsies demonstrate focal/diffuse mesangial proliferation that may be accompanied by glomerular crescent formation. Direct immunofluorescence in kidney reveals diffuse mesangial deposits of IgA and sometimes C3 and properdin.

Clinical manifestations of HSP include:

1) *Purpura,* which tends to resolve more quickly with bed-rest and may reappear in fresh crops with ambulation. The purpura may be preceded by arthritis or gastrointestinal complaints for several weeks, delaying the correct diagnosis.
2) *Arthritis* which is self-limited and non-deforming and is the second most common clinical manifestation. Similar to the purpura, the arthritis tends to lessen with bed-rest and exacerbate with ambulation.
3) *Gastrointestinal involvement*, usually of the jejunum and ileum, is manifested as colicky abdominal pain, vomiting, and/or bleeding, resulting from edema of the bowel wall and hemorrhage secondary to vasculitis. GI symptoms occurring before the onset of the rash may mimic inflammatory/surgical diseases of the bowel leading to invasive diagnostic procedures or exploratory surgery. In 1-5% of children, intussusception (usually ileo-ileo unlike typical ileo-colic) is a rare serious complication which can be diagnosed via abdominal ultrasound. Air/barium enema should be avoided because of an elevated risk of intestinal perforation. Other potential complications include acute appendicitis, bowel ischemia/infarction, intestinal perforation, fistula formation, pancreatitis, hydrops of the gallbladder, and pseudomembranous colitis. Decreased levels of factor XIII (fibrin stabilizing factor) have been found in patients with GI pain/bleeding.
4) *Nephritis* secondary to mesangial IgA deposition is manifested by hematuria. Up to 40% of patients have gross hematuria that may be in conjunction with proteinuria in 2/3 of patients. Unlike arthritis or abdominal pain, it is very rare for nephritis to precede the purpura. In fact, onset of nephritis may be delayed for weeks/months [uncommon after 3 months]. Significant risk factors for developing nephritis include severe abdominal

pain, persistent purpura and decreased factor XIII levels. Nephritis is the most common chronic manifestiation of HSP, especially in adults. Thirty to fifty percent of patients will have persistent urinary abnormalities and 1% will progress to end stage renal disease. Fifty percent of children with nephritis associated with nephrotic syndrome may progress to renal insufficiency. The severity of the renal disease and outcome correlates with the renal histopathologic changes. Crescent formation in >50% of glomeruli is associated with a poor prognosis manifested by significant proteinuria, hypertension, renal insufficiency, and end stage renal disease. HSP has been demonstrated to recur in transplanted kidneys, more likely in living related donor kidneys than in cadaveric kidneys, suggesting a genetic predisposition to the development of HSP nephritis. It is controversial whether early corticosteroid treatment may prevent the delayed appearance of nephritis.

5) *Orchitis* must be distinguished from the more serious testicular torsion.

Treatment modalities include:

1) *Corticosteroids* may ameliorate arthritis and GI symptoms but have no appreciable effect on the purpura, duration of illness or frequency of recurrences. High dose IV pulse methylprednisolone (30 mg/kg/day x 3 days) followed by oral corticosteroids with an immunosuppressive agent (azathioprine or cyclophosphamide) may be useful for severe nephritis thereby preventing progression of the disease.
2) *Dapsone* may act by inhibiting IgA neutrophil interactions thereby having a beneficial effect on the purpura and shortening duration of disease.
3) *Plasmapheresis* may be helpful with rapidly progressive HSP glomerulonephritis.

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Case # 17

CHICAGO DERMATOLOGICAL SOCIETY
RUSH UNIVERSITY MEDICAL CENTER
CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Arthur Rhodes, MD and Rachel Altman, MD

History: This 32 year old African American man with HIV [diagnosed 1998, CD4 count 504, Viral load 111,456 on 2/6/03] presented with a one year history of asymptomatic 1-2 mm flesh colored papules located on his external ears, neck and temporal forehead. The lesions appear to wax and wane in size and numbers of lesions. Therapy using topical triamcinolone 0.1% ointment and 2.5% hydrocortisone creams have been ineffective.

Past Medical History: HIV (diagnosed 1998, last CD4 count 504 MM^3, Viral load 111,456/ml on 2/6/03)
Epilepsy

Physical Findings: External ears, neck and temporal forehead – numerous flesh colored 1-2 mm papules without scale, erythema, or umbilication.

Laboratory Data: RPR – non reactive (3/11/04)
WBC 4.8 x 10-3/UL (5-13), Hgb 15.4 g/dl (11.5-13.5), Hct 45.5% (34-40), Platelet 121,000 with normal differential; Electrolytes, BUN/Creatinine, glucose and liver function tests within normal limits (2/6/03)
Hepatitis C – non reactive (1/9/03)

Biopsy Description: 12/29/03 – Left ear posterior pinna- Epidermis shows a loss of rete ridges. There is a granulomatous infiltrate within the dermis extending to the base of the specimen. Polariscopic examination with light microscopy did not reveal foreign material. A colloidal iron stain revealed mucin deposition within the center of a palisaded granuloma.

Diagnosis: **Granuloma Annulare, Generalized (in the setting of HIV)**

Present Course and Therapy: Lesions have remained stable, unresponsive to therapy.

Discussion: Granuloma annulare is a benign, cutaneous, inflammatory disorder of unknown etiology that is usually asymptomatic or slightly pruritic, and self-limited. There is a higher female incidence, except in HIV associated GA where a strong male predominance exists. Lesions are characterized by erythematous or flesh colored dermal papules in an annular configuration. However, lesions may exist in several other clinical forms including linear, disseminated (generalized), subcutaneous, papular, perforating, and patch presentations. GA was first noted in two homosexual men with AIDS by Penneys and Hicks in 1985. Approximately 40 other known cases of HIV-associated cases of GA have been described to date (predominantly generalized GA). The prevalence of GA in HIV disease is unknown. The differential diagnoses include infections, granulomatous drug reactions, granulomatous lymphoproliferative processes, and lichenoid and granulomatous dermatitis of AIDS. Generalized GA presents with hundreds of 1-2 mm skin-colored papules. This variant has

been associated with an increased prevalence of HLA-Bw35 and A31. Possible associated diseases with disseminated GA include diabetes mellitus and malignancy (breast, lung, colon, prostate, thyroid).

Classically, the histopathologic appearance of GA includes superficial and mid-dermal foci of mucinous degeneration of collagen (necrobiosis) surrounded by a palisading lymphohistiocytic granulomatous infiltrate. Occasionally, the infiltrate is interstitial rather than granulomatous. Collodian iron and alcian blue stains reveal increased mucin deposition.

The etiology of GA is unknown, although several factors have been proposed. These factors include ultraviolet light, arthropod bites, thyroiditis, viral infections (HIV, HZV, EBV), and trauma. The pathogenesis is also unknown but the following hypotheses have been proposed: 1) vasculitis causing necrotic changes in dermal blood vessels, 2) trauma-induced primary necrobiosis, 3) monocyte release of lysosomal enzymes causing necrobiotic degeneration, 4) type IV lymphocyte mediated delayed hypersensitivity reaction causing degenerative changes.

Spontaneous resolution has been described in HIV associated GA as the immune status improves. Treatments are largely ineffective for generalized GA. Treatments have included dapsone, high dose niacinamide, chlorambucil, systemic glucocorticosteroids, antimalarials, and potassium iodide. Resolution of HIV-associated GA has been noted with antiretroviral zidovudine therapy.

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Case # 18

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CHICAGO, ILLINOIS
MAY 19, 2004

CASE PRESENTED BY: Arthur R. Rhodes, M.D. and Alix J. Charles, M.D.

History: This 69 year old African American man presented with a four year history of leg swelling, greater on the right than the left. Swelling, pain, and itching would become more prominent when the patient stood. These symptoms would subside when at rest. The patient denied any history of trauma to the legs, and the pain was not exacerbated by ambulation.

Past Medical History: Hypothyroidism with history of Grave's disease. Hypertension. Otherwise unremarkable.

Physical Findings: Exopthalmos. Bilateral legs display diffuse woody induration with hyperpigmentation. Indurated nodules are also present. Pulses are symmetric and normal in magnitude.

Laboratory Data: Vascular studies of the legs reveal prominent lymph node formation in the right groin with dilated lymphatic channels within the right calf. There is no evidence of acute deep venous thrombosis.

Biopsy Description: Right leg: mild superficial and deep lymphoplasmacytic perivascular infiltrate with "looseness" of collagen bundles. Abundant mucin deposition is confimed by alcian blue and colloidal iron stains.

Diagnosis: **Thyroid Dermopathy** (with lymphatic obstruction)

Present Course and Therapy: The patient was fitted with compression stockings which slightly decreased the swelling and pain.

Discussion: Thyroid dermopathy, or localized myxedema, is an uncommon finding in autoimmune thyroid disease. Approximately 0.5-4.3% of patients with thyrotoxicosis, and 15% of patients with Graves' ophthalmopathy, will develop this condition. Because the condition typically involves the anterior legs, the term pretibial myxedema is oftentimes used as a descriptor. Lesions can also be seen on the arms, shoulders, head and neck. The pathogenesis is not known.

Clinical presentation most often consists of bilateral, asymmetric raised firm plaques and nodules with a pink to purple-brown color. Woody induration or a "peau d'orange" appearance is occasionally seen. Rarely, patients present with an elephantiasis form consisting of nodules and lymphedema. Histological evaluation reveals increased mucin deposition in the dermis. Large amounts of glycosaminoglycans are dispersed diffusely throughout the reticular dermis, leading to separation of collagen bundles. Fibroblasts are often stellate-shaped and increased in number.

Treatment of thyroid dermopathy is challenging. Mid to high potency corticosteroids under occlusion or intralesional corticosteroids have been reported to be effective in some patients. Additionally, use of compression stockings has also been useful, especially when lymphatic compromise is suspected. Systemic corticosteroids and cytotoxic therapy have been used for treatment of ophthalmopathy with incidental improvement in dermopathy. Because of the high rates of recurrence, surgical intervention is not advised.

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Case # 19

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MAY 19, 2004

CASE PRESENTED BY: Arthur R. Rhodes, M.D. and Michael K. O'Donoghue, M.D.

History: An 8 year old Hispanic girl has had two years of mildly pruritic, well demarcated hypopigmented patches with clusters of abundant follicular papules, each with a central keratinous spine, on the torso, legs and arms. Lesions began on the arms, legs, and finally involved the torso. Pruritus has been exacerbated with exercise and warm weather. Lesions have been unresponsive to six months of Protopic ointment 0.1% prior to being seen at RUSH.

Past Medical History: Non-contributory

Physical Findings: Arms, legs and lower back. There are well demarcated hypopigmented patches composed of abundant discrete follicular papules, each papule notable for a central keratinous spine.

Laboratory Data: None

Biopsy Description: None

Diagnosis: **Lichen Spinulosus**

Present Course and Therapy: There has been minimal improvement using low potency topical corticosteroids.

Discussion: Previously known as keratosis follicularis spinulosa, lichen spinulosus is a benign follicular eruption classified among the follicular keratoses. The etiology is unknown. Lichen spinulosus has been reported in association with HIV infection, drug reaction (omeprazole), Hodgkin's disease, Crohn's disease, syphilis, and as an id reaction to fungal infections.

Lesions of lichen spinulosis consist of small spinous papules grouped in patches measuring 2-5 cm in diameter. Individual papules tend to be flesh colored but may be slightly erythematous and bear a hairlike, horny spine that protrudes approximately 1 to 2 mm above the skin surface. Lesions are described as having a "nutmeg-grater" consistency. Affected areas are frequently symmetrical and include the neck, buttocks, abdomen, knees, thighs, popliteal fossae, and extensor aspects of the arms. About one-third of patients have mild to moderate pruritus. On microscopic examination, lichen spinulosus shows dilated hair follicles filled with a keratotic plug. Surrounding the affected follicles is a lymphohistiocytic inflammatory infiltrate that may be scattered throughout the dermis. Hyperkeratosis, parakeratosis, and acanthosis may also be found. Under direct immunofluorescence, a fine granular dermal-epidermal immunofluorescent band may be seen using anti-serum to IgM. The differential diagnosis includes keratosis pilaris, pityriasis

rubra pilaris, psoriasis, nummular eczema, miliary papular syphilis, lichen planopilaris, and frictional lichenoid eruption. Treatment has centered on keratolytics and emollients. The prognosis of lichen spinulosus is variable. Some lesions may persist for months to years with little or no change, while in other patients, the disease will remit and recur.

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CASE PRESENTED BY: Arthur R. Rhodes, M.D. and Michael K. O'Donoghue, M.D.

History: A 3 year old Hispanic girl presented with an asymptomatic congenital mass on the left side of her face. The mass has gradually enlarged, and there have been no neuromuscular or airway complications. She received treatment with interferon and OK-432 without resolution or improvement in the size of the lesion.

Past Medical History: The child was born after a full term gestation. No significant medical problems were elicited.

Physical Findings: There is a large, soft, and compressible mass involving the left cheek, left neck, and left postauricular area. The mass transilluminates with light. There is no surface change. The eyes, ears, teeth and tongue were normal in appearance.

Laboratory Data: 09/16/2003: Magnetic Resonance Imaging (MRI) Orbit and Face: A large mass arises from the left side of the face in the malar area, encases the left orbit, zygoma, maxilla, external ear, left mandible and extends to the left submental area across the midline to the right and extends over the chest wall anteriorly.
04/12/2004: MRI Orbit and Face: There is an interval decrease in size of the mass lesion compared to the MRI obtained on 09/16/03.

Biopsy Description: 02/19/04: Left neck: Fibrous tissue with numerous dilated lymphatic channels, edema, and chronic inflammation, consistent with cystic hygroma.

Diagnosis: **Cystic Hygroma**

Present Course and Therapy: The child was referred to a pediatric otolaryngologist. She underwent left radical parotidectomy, left neck dissection, removal of the cystic hygroma, with tracheostomy placement, on 02/19/2004.

Discussion: Lymphangiomas can be classified as: 1) lymphangioma simplex, which is comprised of small lymphatic capillaries; 2) cavernous lymphangioma, made up of larger channels; and 3) cystic lymphangioma, which corresponds to cystic hygroma. The malformation in the lymphatic system is believed to develop prenatally from a congenital blockage or arrested development of the primordial lymph channels. Alternatively, cystic hygroma may arise from a failure of the juguloaxillary lymphatic sac to drain into the internal jugular vein. In 65-75% of patients, lesions are present at birth, and in 80-90% by the second to third year of life.

The most prominent sign of lymphangiomas is a mass. In cystic hygoma, 90% of lesions are located to the cervical region. The characteristic appearance is a soft, somewhat doughy mass that transilluminates. These lesions are composed of dilated lymphatic channels with one or two endothelial layers, with or without an adventitial layer. On computed tomography (CT) images, cystic hygroma tends to appear as poorly circumscribed, multiloculated, hypoattenuated mass with a characteristic homogenous fluid attenuation.

Treatment for cystic hygroma is dependent on clinical presentation. If a patient presents with life threatening symptoms such as macroglossia with dysphagia or with airway obstruction,

surgical intervention is warranted. When a mass is the only sign, observation is recommended until the child is at least two years of age. If the mass does not regress or if it enlarges, imaging studies with either CT or MRI should be completed in order to ascertain the anatomical sites of involvement. If the lesion is below the level of the hyoid and predominantly in the posterior triangle, surgical excision is the preferred course. If lesions are above the hyoid and invade the oral and pharyngeal mucosa, intralesional injections of OK-432 may be a better choice of management. OK-432 is a sclerosing agent derived from a non virulent strain of Streptococcus pyogenes treated with penicillin G. OK-432 decreases the size of the lesion by increasing the endothelial permeability and accelerating lymph drainage, leading to shrinkage of the cystic spaces. If lesions develop later in life, observation is recommended because the majority of these lesions will spontaneously regress. Morbidity and mortality associated with cystic hygromas are related to lesion size and patient age at onset. Large lesions in younger patients are the most difficult to manage.

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