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TABLE OF CONTENTS

CASE#	TITLE	PAGE#
1	Mutilating Palmoplantar Keratoderma with Periorificial Keratotic Plaques (Olmsted Syndrome)	1
2	Agminated Nevi Acquired in Childhood	4
3	PHACES Syndrome	6
4	Ehlers-Danlos Syndrome, Classical Type, with a Slow-Healing Wound and <i>Aspergillus fumigatus</i> infection	8
5	UNKNOWN CASE	10
6	Malignant Pyoderma	11
7	Generalized Morphea with Bullous Lesions	13
8	Mycosis Fungoides Initially Presenting as a Rosacea-Like Granulomatous Dermatitis	17
9	Nephrogenic Systemic Fibrosis	19
10	Pagetoid Reticulosis	22
11	Ectodermal Dysplasia with Immunodeficiency, Secondary to NEMO Mutation	24
12	Setleis Syndrome	26
13	Costello Syndrome	28
14	Linear IgA Bullous Dermatitis	30
15	Bullous Sweet's Syndrome with Fatal Neutrophilic Alveolitis	32
16	Noduloulcerative Syphilis	34
17	Neutrophilic Eccrine Hidradenitis	36
18	Quinacrine-Induced Lichenoid Drug Eruption with T-cell Clonality	38
19	Intravascular B-cell Lymphoma, Large-cell Type	41
20	Palmar-plantar Erythrodysesthesia Syndrome (PPES)	43

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Patient A

HISTORY OF PRESENT ILLNESS

The patient is a 31-year-old woman who initially presented to Children's Memorial Hospital (CMH) at 11 years of age with a history of dry kinky hair since birth, cheilitis, and a progressive, painful palmoplantar keratoderma (PPK) with flexion contractures and deformity since the age of three years. Prior treatments include 40% urea in topical emollients, repeated paring procedures, and high-dose vitamin A, which were of little benefit. She started isotretinoin at nine years of age. Skin grafting of her feet from the thigh was also very painful and unsuccessful. She was not seen between 11 and 19 years of age. At that time she returned to CMH, where a diagnosis of mutilating palmoplantar keratoderma was made (Olmsted syndrome). She was switched to etretinate and subsequently to acitretin, on which she reports some improvement. Her PPK remains severe but becomes worse when retinoids are tapered or discontinued. She continues to have regular paring, but notes rapid return of the painful keratoderma.

PAST MEDICAL HISTORY

Bilateral congenital hip dysplasia with severe osteoarthritis of the left hip, reactive gastropathy, hypertriglyceridemia, osteoporosis of lumbar spine, and nicotine dependence

MEDICATIONS

Acitretin

FAMILY HISTORY

She is the first affected member in the family. She has an affected daughter with onset of hair loss as a toddler.

PHYSICAL EXAM

There are well-demarcated, yellow, keratotic plaques with surrounding erythema and tenderness on the palms and soles. Hands and feet are also notable for flexion contractures and marked deformity. Toenails are markedly dystrophic. There is marked cicatricial alopecia with dry, kinky hair and moderate angular cheilitis with fissuring.

HISTOPATHOLOGY

449, University of Chicago, 1981 (plantar aspect of foot): Epidermis with hyperkeratosis, acanthosis, and perinuclear vacuolization of many keratinocytes. Dermis was unremarkable.

489, University of Chicago, 1981 (scalp): Epidermis unremarkable. The dermis, including pilosebaceous follicles, is normal.

Light microscopic examination of hair mounts demonstrated that about 70% of the hair was thin but showed no shaft abnormality.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Gene analysis for keratin type 1 and 10, comprehensive metabolic panel, and calcium

Patient B

HISTORY OF PRESENT ILLNESS

The patient is a 13-year-old girl (the daughter of patient A) who was initially seen as a 19-month-old infant with thin, stiff, brittle, sparse blond hair; the remainder of her examination was normal at that time. She was subsequently seen at eight years of age. By this time, she had developed focal heaped up keratoderma of the palms and soles, early flexion deformities of the hands, horny keratotic plaques on the elbows and knees, small keratoses at the angles of the mouth, hypotrichosis of the scalp, and onychodystrophy of all nails. Her PPK was treated by weekly paring procedures by a podiatrist, and intermittently by a plastic surgeon under general anesthesia.

PAST MEDICAL HISTORY

None

MEDICATIONS

Lorazepam, gabapentin, and morphine sulfate

FAMILY HISTORY

Affected mother

PHYSICAL EXAM

On the palms (especially the thenar eminence) and soles there are well-demarcated, yellow, keratotic plaques with surrounding erythema and tenderness. The feet reveal medial deviation of the first and second toes with overlapping of digits, mild flexion contractures, and dystrophic nails. There is alopecia with dry, kinky hair.

HISTOPATHOLOGY

None

DIAGNOSIS

Mutilating palmoplantar keratoderma with periorificial keratotic plaques (Olmsted syndrome)

TREATMENT AND COURSE

Patient A remains on acitretin 50 mg daily and continues to receive weekly paring procedures by her podiatrist, with biyearly surgical debulking procedures. She is also taking lorazepam, gabapentin, and morphine sulfate as needed for pain. She underwent extensive debulking on 9/8/06 and subsequently began therapy with the epidermal growth factor receptor (EGFR) inhibitor erlotinib at a dose of 100 mg daily. Patient B has never been on any medical therapy. She continues to pare her PPK herself with alcohol and scissors weekly with yearly surgical debulking procedures. She uses oxycodone as needed for pain.

DISCUSSION

Olmsted syndrome is a rare disorder of keratinization characterized by a symmetrical mutilating palmoplantar keratoderma and hyperkeratotic plaques around body orifices. The keratoderma usually begins in early childhood and worsens as the child starts to walk and grasp. The course is chronic and progressive as patients develop flexion contractures, ainhum-like constrictions, and spontaneous autoamputation of digits resulting in significant disability. Pain, pruritus, fissures, recurrent intertrigo, and

microbial superinfection are frequent and further complicate the course of this debilitating disease.

Associated clinical manifestations are variable and include: diffuse or partial alopecia, chronic paronychia, onychodystrophy, urticaria, follicular hyperkeratosis, oral leukokeratosis, anhidrosis of the palms and soles, and short stature. There have been many reported systemic associations including large joint laxity, absent premolar teeth, high frequency hearing loss, corneal epithelial dysplasias, and primary sclerosing cholangitis. However, their relationship to Olmsted syndrome is uncertain. In addition, there have been several reports of the development of squamous cell carcinoma as well as malignant melanoma in the hyperkeratotic lesions of Olmsted patients.

The genetic defect in Olmsted syndrome has not been determined and the mode of inheritance is unclear. Our cases appear to represent autosomal dominant inheritance. Two other families with an autosomal dominant inheritance pattern have been described in the literature, but with variable penetrance. Immunohistochemical staining has shown an abnormality in keratin expression, specifically of keratins 5 and 14 in the suprabasilar epidermis, suggesting that the involved epidermal area remains in an immature proliferative stage. This pattern has also been found in a variety of other hyperproliferative disorders, including psoriasis, verruca, and seborrheic and actinic keratosis.

Treatment of Olmsted syndrome is often disappointing. Topical therapy with retinoic acid, corticosteroids, emollients, and keratolytics may offer some temporary symptomatic relief, but is grossly insufficient. As in our patients, frequent paring of the keratosis does decrease pain and improve hygiene and related secondary superinfection. Most experiences with skin grafting are unsuccessful, as the hyperkeratosis recurs on the grafted site with the added risk of hyperkeratosis developing at the donor site as a result of Koebner phenomenon. Systemic retinoids have been the most useful agents to date. They induce cellular differentiation, are antiproliferative and anti-inflammatory, and normalize keratinization. However, their effects are variable and limited, in some cases having no effect at all. Our patient has been on systemic retinoid therapy for over 20 years with considerable persistent keratoderma, although she is much worse without the medication.

There is no report on the use of EGFR inhibitors in Olmsted syndrome, but there are reports of the inadvertent clinical improvement of psoriasis in cancer patients being treated with EGFR inhibitors. Erlotinib works by inhibiting epidermal growth factor receptor (EGFR) tyrosine kinase activity. Activation of EGFR in epidermal keratinocytes promotes cellular proliferation, differentiation, and cell survival. We hypothesize that treatment with an EGFR inhibitor will result in clinical improvement, and present this case for discussion of possible novel therapeutic approaches for Olmsted syndrome.

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Patient A

HISTORY OF PRESENT ILLNESS

The patient is a healthy 29-year-old man who developed an abrupt eruption of numerous nevi in his early childhood years. He was apparently born with two small "patches" on his back, but rapidly developed multiple nevi diffusely over his back, reportedly after sun exposure. One nevus was biopsied over 20 years ago and was benign by report; he had not seen a dermatologist since that time. He denied any changing or symptomatic lesions.

PAST MEDICAL HISTORY

Wheat intolerance (not celiac disease) and status post femoral rod placement

FAMILY HISTORY

Psoriasis in several family members, but otherwise noncontributory

PHYSICAL EXAM

On the back, there are hundreds of medium to dark brown macules and thin papules, most of which are entirely benign-appearing with regular borders. Woods lamp did not accentuate background pigmentation. On the left flank and left mid paraspinal areas, there are two variegated and regressing macules under dermoscopy.

HISTOPATHOLOGY

DP 06-1552-I (left flank): The epidermis shows mild elongation of the rete ridges with many irregular nevomelanocytic nests and focal bridging between the rete ridges. Shoulder extension of the nests is also identified. The nevomelanocytes have abundant cytoplasm, and the nuclei are slightly large with occasional hyperchromasia and prominent nucleoli. The stroma shows concentric fibroplasia. Nuclear atypia is mild.
DP 06-1552-II (left mid paraspinal): There are numerous single and nested melanocytes along the dermoepidermal junction and upper dermis showing normal maturation and only minimal nuclear atypia. There are numerous lymphocytes involving the intraepidermal and dermal compartments. This lesion shows some features of a halo nevus.

Patient B

HISTORY OF PRESENT ILLNESS

The patient is an eight-year-old Caucasian boy with a history of Langerhans cell histiocytosis (LCH) diagnosed in infancy who developed multiple clustered nevi at the age of six years. Initial presentation of LCH at five months of age included dermatitic skin lesions, liver and mild lung disease, but no bone marrow involvement, and he was treated for six months with vinblastine and prednisone. He was retreated for disease recurrence when he was one year of age, and never received radiation. Over one year after completing therapy, he began to develop asymptomatic freckle-like lesions on his axillae, groin, and arms, which by his parents' report are sites of his previous cutaneous histiocytosis. He has continued to develop new lesions.

PAST MEDICAL HISTORY

Langerhans cell histiocytosis, status post chemotherapy

FAMILY HISTORY

No family history of melanoma

PHYSICAL EXAM

There are clusters of 1-2 mm brown macules, some in confluent patches, at the bilateral inguinal creases, left axilla, and inferior abdomen, all entirely benign-appearing.

HISTOPATHOLOGY

None

DIAGNOSIS

Agminated nevi acquired in childhood

TREATMENT AND COURSE

Both patients are followed regularly, but no additional work-up has been initiated.

DISCUSSION

The term "agminated," derived from the Latin "agmen" for aggregation, describes a clustering of lesions, and in most dermatologic literature, has been used to describe grouping of Spitz nevi. Cases of agminated nevi, both benign and dysplastic, have been reported, though the incidence appears much less common. It is thought that this patterning represents a loss of heterozygosity for one of the genes responsible for development of nevi within the affected skin, though specific details regarding the etiology of such lesions are not well defined. The main clinical differential diagnosis includes the nevus spilus, wherein background pigmentation should be visible on Wood's light examination. Agminated nevi have been documented as both congenital and acquired (usually during the teenage years), but significant associations or risk of malignancy have not been reported. However, there is some confusion in the literature with regard to agminated versus segmental dysplastic nevi (i.e. segmental or zosteriform distribution of dysplastic nevi without classical clustering pattern), as the latter seems to carry a higher risk for the development of melanoma. It is important to note that nevus spilus can involve a substantial part of the skin, as in our first patient's entire back, and that nevus spilus has been associated rarely with melanocytic dysplasia and melanoma. Finally, the phenomenon of eruptive nevi with immunosuppression is well described, however we know of no report of eruptive agminated nevi under similar circumstances.

We present these patients as two different and intriguing presentations of agminated or speckled nevi, both appearing during childhood. In the first patient, the development of the lesions reportedly followed sun exposure, while in the second, the eruption occurred one year following chemotherapy, and may have involved areas previously affected by LCH. In the first patient, mild dysplastic changes have been documented within the area of involvement, while in the second patient, we believe biopsy has not yet been indicated. We present these cases as examples of unusual nevi patterning, to discuss clinical monitoring and risk of malignancy, and to propose that such lesions may occur following immune suppression or other yet undefined triggers.

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HISTORY OF PRESENT ILLNESS

The patient is a four-week-old girl born with multiple cardiac abnormalities who was admitted to the pediatric intensive care unit with hematochezia and severe anemia. CT examination of the abdomen revealed extensive hemangiomas in her liver, spleen, pancreas, and intestines. The dermatology service was consulted for assistance in the management of her hemangiomas, and upon examination, a faint erythematous patch was noted on her left upper face.

PAST MEDICAL HISTORY

Born at 36 weeks status post induction for maternal hypertension, coarctation of the descending right thoracic aorta, right cervical aortic arch, isolated left subclavian artery, ventricular septal defect, atrial septal defect, and patent ductus arteriosus

MEDICATIONS

Furosemide and lansoprazole

FAMILY HISTORY

No family history of vascular lesions

PHYSICAL EXAM

On the left periorbital area and temple there is a segmental, faint, telangiectatic patch that extends into the temporal scalp and is studded with vascular papules. The lower lip, tongue, and lower gingivae exhibit vascular macules and papules. The patient was also noted to have a hoarse cry.

LABORATORY AND STUDY RESULTS:

The following were negative or within normal limits:

Comprehensive metabolic panel, thyroid stimulating hormone; Ophthalmologic exam

The following were abnormal:

Hemoglobin 4.4, hematocrit 13.1, white blood cell count 15.6, platelets 455,
CT/MRI of the brain: Subacute infarct in the right frontal lobe, abnormal enhancement in the left suprasellar/interpeduncular cistern and right foramen of Luschka, possibly representing abnormal veins or hemangiomas. Multiple anomalies were noted in the intracranial and neck vessels. No posterior fossa malformations are present,
Direct Laryngoscopy: Dilated vessels in the anterior and posterior subglottic larynx, paralyzed right vocal cord, and right bronchomalacia

DIAGNOSIS

PHACES syndrome

TREATMENT AND COURSE

The patient was started on prednisolone 2 mg/kg/day, which was eventually increased to 3 mg/kg/day. By day six of steroid therapy, her hematochezia had ceased and her hemoglobin was stable. She was discharged home with scheduled follow-up.

DISCUSSION

The acronym PHACE syndrome describes the association of large facial hemangiomas with other cardiac, neurologic, and ophthalmologic anomalies. The findings include posterior fossa malformations, large segmental hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities. The term PHACES syndrome is sometimes used when sternal abnormalities or a supraumbilical raphe are present. Diagnosis of PHACES syndrome requires the presence of a segmental hemangioma and one other anomaly.

The segmental facial hemangiomas described involve cutaneous segments on the face that do not correlate with facial dermatomes or lines of Blaschko. A photographic review of infantile hemangiomas resulted in four primary segments: segment 1 (frontotemporal), segment 2 (maxillary), segment 3 (mandibular), and segment 4 (frontonasal). These segments are similar to facial prominences described in embryology, with the exception of frontonasal, which is usually shown to also extend laterally. The posterior fossa malformations described include Dandy-Walker malformations, ventriculomegaly, arachnoid and choroid plexus cysts, and hypoplasia or agenesis of cerebellum, corpus callosum, cerebrum, and septum pellucidum. The arterial anomalies include aneurysms and anomalous branches of the ICA, cerebral arterial stenosis and retro-orbital and parasagittal AV malformations. Cardiac anomalies include patent ductus arteriosus, ventricular septal defects, atrial septal defects, and pulmonary stenosis. Eye anomalies observed include microphthalmos, optic atrophy, and iris hypoplasia.

The etiology and pathogenesis of PHACES syndrome is currently unknown, but it may be secondary to an insult occurring in the first trimester, giving rise to several associated structural anomalies. Evidence for this includes the segmental nature of the hemangiomas, correlation of segment with extracutaneous anomalies, and the finding of a Dandy-Walker malformation on prenatal ultrasound as early as 12 weeks. The large proportion of female infants affected suggests either an X-linked inheritance or lethality in males. Complications of large segmental facial hemangiomas include visual compromise, ulceration, infection, permanent anatomic deformity, and interference with feeding. Treatment includes oral steroids at dosages of 2-4 mg/kg/day, interferon, vincristine and topical therapies. Patients with possible PHACES syndrome should obtain careful neurologic, cardiac, and ophthalmologic evaluation. Otolaryngologic evaluation should also be considered in patients with S3 hemangiomas or upper airway obstruction.

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HISTORY OF PRESENT ILLNESS

The patient is a nine-year-old girl with classical Ehlers-Danlos syndrome who presented with a wound on the left lower leg one week after injuring it on a wooden fence. Immediately after the injury, she went to a local emergency room where she was noted to have a 7.5cm full-thickness laceration. Sixteen superficial 4-0 nylon sutures were used to close the wound; deep sutures were attempted but were unable to be placed. She was given oral amoxicillin and topical bacitracin ointment. The wound was healing poorly, and one week after this event, she presented to the dermatology clinic where half the sutures were removed and therapy with cephalexin was initiated. On subsequent follow-up one week later, the wound was noted to be healing slowly and showed considerable yellow discharge. The patient was not febrile, and no palpable lymphadenopathy was noted. She was advised to start compresses with Burrow's solution and apply topical mupirocin to the wound. She was also advised to use Prisma, which is a collagen with Silvadene matrix, to encourage wound healing. A wound culture was sent and one week later, the culture was positive for *Aspergillus fumigatus*. At this time, the wound showed mostly healthy granulation tissue, but there was a focal dark area on the superior end of the wound.

PAST MEDICAL HISTORY

Ehlers-Danlos syndrome, classical type

FAMILY HISTORY

No family history of easy bruisability, hyperextensibility of skin and joints, or poor wound healing

PHYSICAL EXAM

On the left anterior shin there is a violaceous-to-black gaping wound about 1cm in width. The edges are not inflamed, and there is no drainage or yellow crusting. One superficial hemorrhagic bulla is present on one edge of the wound. The right anterior shin has an old fishmouth-like scar as well as hyperpigmentation.

DIAGNOSIS

Ehlers-Danlos syndrome, classical type, with a slow healing wound and *Aspergillus fumigatus* infection

TREATMENT AND COURSE

Although the wound was not frankly necrotic, infectious disease consultants were concerned that *Aspergillus fumigatus* might be a true pathogen. Therefore the patient was given voriconazole 100mg bid orally for four weeks. Over the next two months, the patient's wound healed completely.

DISCUSSION

The classical type of Ehlers-Danlos syndrome (EDS) is characterized by soft, velvety, and hyperextensible skin, joint hypermobility, easy bruising, and delayed wound healing with atrophic scars that have a papyraceous or "cigarette-paper-like" appearance. Classical EDS is usually inherited in an autosomal dominant fashion, and about 50% of cases are caused by mutations of the genes encoding type V collagen,

COL5A1 and *COL5A2*. In a substantial portion of patients with classic EDS, the molecular defect has not been identified. Collagen plays a critical role in wound healing and during the initial phase of wound repair, granulation tissue is initially comprised of large amounts of type III collagen. Over a period of a year or more, remodeling occurs, where type III collagen is gradually replaced by type I collagen and results in increased tensile strength of the scar.

Although there is no report of experimental models of wound healing with deficiency of collagen V, it can be surmised from immunohistochemical studies that it plays a role in early wound healing. Type V collagen expression was found, albeit in lower levels than type III collagen, as soon as three days into wound healing, and it was strongly expressed in blood vessel walls in granulation tissue. The delay in wound healing results in longer periods of compromise to the skin barrier and this in essence increases the risk for infection. In our patient, culture of the wound drainage revealed no bacteria but instead grew *Aspergillus fumigatus*. Fungi of the *Aspergillus* genus are commonly found in the soil and in decomposing vegetation. They are frequent opportunistic pathogens in immunocompromised patients, second only to *Candida*. However infection is rare in immunocompetent hosts. Primary cutaneous infection with *Aspergillus* is seen with inoculation of the organism in damaged skin, such as maceration from tape or intravenous catheters sites, in the setting of an immunocompromised state.

Management of our patient included an unexpected complication, as immunocompromise is not a feature of EDS, yet our patient had at best, a colonization, or at worst, a primary cutaneous infection with *Aspergillus fumigatus*. In order to promote wound healing and to prevent any potential for dissemination of this organism, treatment with voriconazole was initiated under the infectious disease team's recommendations. Our patient is presented to emphasize that special attention to surgical care is important to reduce potential complications in management of children with skin fragility. General guidelines include the following: 1) dermal wounds should be closed without tension, preferably in two layers, 2) closely placed deep sutures should always be used (some have suggested the placement of nonabsorbent deep sutures to provide long-term support), 3) superficial sutures (twice as many should be used as in normal skin) may need to be left in place twice as long as usual, and 4) fixation of adjacent skin with steri-strips may help prevent stretching of the scar.

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HISTORY OF PRESENT ILLNESS

The patient is a 51-year-old man with no significant past medical history who was admitted to hospital for evaluation of a rapidly progressive, painful, ulcerative eruption on the face and neck that began five weeks after a sore throat and stomach cramping. Prior to admission, he was treated with numerous oral antibiotics and prednisone (up to 120 mg daily) for four weeks. While on this regimen the eruption progressed and he developed similar ulcerative lesions on the trunk, arms and thighs. The patient was beginning to develop difficulty breathing due to partial destruction of the nasal cartilage.

PAST MEDICAL HISTORY

Hepatitis A and partial retinal detachment

MEDICATIONS

Prednisone, oxycodone, and esomeprazole

ALLERGIES

No known drug allergies

PHYSICAL EXAM

There are numerous papulopustules and ulcers arising on erythematous to violaceous bases, ranging in size from 2mm to 2cm, on the head, neck, upper trunk, and extremities. Some have necrotic, crusted centers with boggy, violaceous borders. In addition, shallow ulcers are present on the tongue, pharynx and nasal mucosa.

HISTOPATHOLOGY

DP 06-1602 (left posterior shoulder): Dense, neutrophilic infiltrate involving the upper dermis with neutrophilic spongiosis and necrotic changes. Vasculitis was not noted. Special stains for fungi and bacteria were negative.

Nasal mucosal biopsy at an outside hospital was negative for granulomatous disease and negative for PAS, acid fast, and Gram stains.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Comprehensive metabolic panel, rheumatoid factor, erythrocyte sedimentation rate, antinuclear antibodies, SS-A, SS-B, complement C3, C4, p-ANCA, c-ANCA, HLA B27, glucose-6-phosphate dehydrogenase, quantitative immunoglobulins, serum and urine electrophoresis, peripheral blood smear, urine analysis, random urine protein, cytomegalovirus titers, urine iodide and bromide levels, bacterial culture of throat and blood, X-ray of neck and chest, CT of the chest, abdomen, and pelvis, esophagogastroduodenoscopy and colonoscopy.

The following were abnormal:

White blood cell count 13.7, neutrophils 83%, C-reactive protein 10.52.

DIAGNOSIS

Malignant pyoderma

TREATMENT AND COURSE

The patient received pulse methylprednisolone 1g daily for five days with minimal improvement. He was discharged home on prednisone 80 mg daily, and shortly after tacrolimus 10 mg and dapsone 100 mg daily were added to the regimen. He markedly improved over one month with a noticeable decrease in the erythema and the size of the ulcers. He was tapered off prednisone over five months. Six months after initiation of therapy, his ulcers have completely healed but have left cribriform scars. All medications have since been discontinued.

DISCUSSION

Malignant pyoderma, first described in 1968 by Perry, is a rapidly progressive ulcerating cutaneous condition of unknown origin that predominantly affects the head and neck of young adults. Malignant pyoderma has been considered to be a distinct entity from pyoderma gangrenosum because of the predominant head and neck location of the ulcers and because the ulcers lack undermining and surrounding erythema. Although the disease is idiopathic in 25-50% of patients, an underlying immunologic abnormality has been suggested as a cause given its frequent association with systemic diseases such as Wegener's granulomatosis, ulcerative colitis, and Crohn's disease. Defects in cell-mediated and humoral immunity as well as neutrophil and monocyte function have been reported, but none of these findings have been demonstrated consistently.

Several therapeutic approaches to malignant pyoderma are beneficial but treatment efficacy remains difficult to evaluate in this disease where the pathogenesis is unknown and the clinical course is unpredictable. There are several available options in the treatment of malignant pyoderma; however no single therapy is universally effective. Proper diagnosis and treatment of an underlying systemic disease, if present, may lead to improvement of cutaneous findings. Treatment with systemic corticosteroids as well as anti-inflammatory and immunosuppressive agents has been beneficial in most patients. However, refractory cases, such as the one reported herein, require alternative therapies. Previous studies has shown that tacrolimus is effective in patients with recalcitrant pyoderma gangrenosum. An alternative treatment in our patient would have been the use of cyclosporine. However, it has been associated with a greater risk of nephrotoxicity in long term use. Our patient had progression of disease while on oral antibiotics and high dose oral prednisone, so we opted for a combination trial of tacrolimus, dapsone and prednisone, which resulted in significant improvement over six months.

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Patient A**HISTORY OF PRESENT ILLNESS**

The patient is a 66-year-old woman who developed tightening of the skin on the right side of her chest in late 2005. Following an initial biopsy, fluocinonide ointment and Aquaphor were used, but the firmness rapidly spread across her chest, back, neck, and arms. She became very tight, stiff, and uncomfortable with itching, burning, and muscle cramps, forcing her to stop work. A repeat biopsy was performed. As a result, she was treated with 20 sessions of oral psoralen ultraviolet A (PUVA), prednisone 5mg, hydroxyzine, fexofenadine, and occupational therapy in addition to her previous topical regimen. However, she noticed no particular improvement in her symptoms.

PAST MEDICAL HISTORY

Breast cancer 1992 status post left mastectomy and chemotherapy, diabetes mellitus, hypothyroidism, hypertension, uterine fibroids, and renal cysts

MEDICATIONS

Aquaphor, fluocinonide ointment, prednisone, hydroxyzine, fexofenadine, furosemide, lansoprazole, levothyroxine, metformin, glimepiride, nisoldipine, labetalol, lorazepam, tramadol-acetaminophen, albuterol/ipratropium inhaler, and fluticasone/salmeterol inhaler

ALLERGIES

Penicillin

FAMILY HISTORY

Daughter has recent onset of aggressive systemic lupus erythematosus, and a cousin also has lupus. Father died of a stroke.

SOCIAL HISTORY

Works as a financial counselor, currently on medical leave. Quit tobacco 20 years ago.

PHYSICAL EXAM

There is shiny, wrinkled, and tightly bound-down skin on the arms, trunk, and thighs. The area at the base of the right breast is so tight and bound down to the chest wall that slight pressure causes a clear fluid nipple discharge. Her abdomen is distended, and there is a 5 cm fluid-filled tan plaque overlying the umbilical area.

HISTOPATHOLOGY

11/8/2005, DC 06-237 (left flank): Central excoriation covered by a serosanguinous exudate. The dermis shows a perivascular lymphohistiocytic inflammatory infiltrate with increased perivascular and interstitial eosinophils. The dermal collagen is slightly thickened and fibrotic.

5/16/2006, DP 06-5982 (right shoulder): Flattening of epidermis with effacement of the rete ridges. Dermis shows marked sclerosis and entrapment of adnexal structures extending into septopanniculus, consistent with morphea.

5/30/2006, DP 06-6591 (umbilicus): Detached epidermis from the dermis, which shows dense fibroplasias while the epidermis shows some reactive change with no malignant features, consistent with bullous scleroderma.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Complete blood count and platelets, complete metabolic panel, renal function, liver function tests, complements. Mammogram and bone scan were negative. CT scan of chest/abdomen/pelvis: old granulomatous disease of her lungs related to prior pneumonia and a pelvic mass, consistent with a fibroid. No evidence of ascites.

The following were abnormal:

Antinuclear antibody 1:80-1:320 (nucleolar)

DIAGNOSIS

Generalized morphea, with bullous lesions

TREATMENT AND COURSE

The patient has continued prednisone 5mg daily, hydroxyzine, fexofenadine, fluocinonide ointment, and Aquaphor. Additional anti-inflammatory agents have included oral erythromycin, which she was unable to tolerate, and colchicine. Her condition has remained unchanged during the last few months. Bath PUVA was discussed with the patient but she has been unable to start this due to her daughter's illness. The patient plans to initiate hydroxychloroquine in the near future.

Patient B

HISTORY OF PRESENT ILLNESS

The patient is a 72-year-old woman who developed swelling, hardness and discomfort of the skin of her neck, arms, and legs in January 2005, associated with fatigue, stiffness, and muscle and foot pain. She was initially evaluated at Rush University and was started on prednisone 60mg daily. The patient presented to Northwestern in January 2006 with a presumed diagnosis of Shulman's syndrome. Since that time, the patient continued to develop diffuse, large (25-40cm) bright red patches, which over a period of two weeks would regress, leaving shiny, wrinkly, slightly tan, bound-down areas.

PAST MEDICAL HISTORY

Previous hysterectomy, thyroidectomy, and corneal surgeries

MEDICATIONS

Prednisone, levothyroxine, and aspirin

ALLERGIES

Penicillin and sulfa

FAMILY HISTORY

Father has diabetes

SOCIAL HISTORY

She is married and is currently retired. She travels a great deal and drinks alcohol socially.

PHYSICAL EXAM

There are shiny, wrinkly, tight, and bound-down areas of skin on the neck, trunk, arms and legs. On the umbilicus there is an 8 cm-wide band of wrinkly, eroded skin superimposed on even more shiny, wrinkly skin of the lower abdomen.

HISTOPATHOLOGY

1/25/2006, DP 06-1080-I (right breast): Dermis shows dense fibroplasia and entrapment of adnexal structures extending into deep reticular dermis, consistent with scleroderma.

1/25/2006, DP001080-06-II (right forearm): Similar to right breast biopsy

8/4/2006, DP 06-9478 (umbilicus): Hyperkeratosis with focal parakeratosis of the stratum corneum. Superficial dermis is edematous and homogenized with dilated vessels. Dermis has dense fibrosis of dermal collagen. Elevation and entrapment of eccrine coils within the dermis. Surface changes most consistent with surface changes of lichen sclerosis et atrophicus and the biopsy is overall consistent with bullous morphea.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Complete blood count with differential (except eosinophils, see below), complete metabolic panel, coagulation parameters, thyroid-stimulating hormone, creatine kinase, aldolase, serum protein electrophoresis, urinalysis, anti-Scl-70

The following were abnormal:

Antinuclear antibody 1:320 in a homogeneous pattern, absolute eosinophilia 1.09

DIAGNOSIS

Morphea and lichen sclerosis et atrophicus overlap

TREATMENT AND COURSE

Initially, the patient was treated with prednisone 60mg daily. She was also started on antihistamines, oral calcitriol, triamcinolone 0.025% ointment, and ultraviolet A to her whole body. Though she reported less pruritus with hydroxyzine, her condition continued to progress. More recently, she has begun therapy with mycophenolate mofetil, and her topical steroid has been changed to betamethasone/calcipotriene ointment. She is still getting UVA therapy 2-3 times per week. Some of her lesions have improved, though she still has hard, bound-down skin on her upper extremities and anterior trunk. The abdominal erosion is still present, though it has partially healed. Hydroxychloroquine will likely be added to her treatment regimen in the near future.

DISCUSSION

Morphea is a disorder of unknown etiology that is characterized by the appearance of immobile, hard, smooth plaques that may appear similar to hidebound skin. It is about two to four times more common in women than in men. By one classification system, morphea can be divided into five categories: localized, generalized, profunda, atrophic, and pansclerotic. In another classification system, subtypes of the disease include plaque, generalized, bullous, linear, and deep. Generalized morphea typically occurs when plaques affect more than two anatomic sites and become confluent.

First reported in 1896, bullous morphea is a rare and aggressive form of scleroderma. It is usually superimposed on the typical plaque form or morphea profunda (which involves deep subcutaneous tissue, including fascia, and can resemble eosinophilic fasciitis). Bulla formation may be attributed to localized trauma or lymphatic obstruction caused by the sclerodermatous process. Fewer than 100 cases have been reported in the world literature.

Clinically, tense subepidermal bullae appear in the presence of indurated plaques with pigmentary change. Fresh plaques are violaceous in color and progressively whiten. These lesions are most common on the lower extremities and inferior abdomen, but may also involve other parts of the trunk, upper extremities, face, or neck. They may be superficial or extend deep into the dermis. Many of these bullae are hemorrhagic in nature. Muscle atrophy may be present, but typically, there is no systemic involvement. Deep biopsy is occasionally needed to make diagnosis. Histologically, findings common to all forms of morphea may be seen, including thickening and homogenization of collagen bundles. As noted above, there are several different mechanisms of bulla formation, and the histology can vary based upon the mechanism. For example, the microscopic appearance of a traumatized area may look similar to lichen sclerosis et atrophicus, while that of lymphatic obstruction looks similar to lymphangiectasias.

Treatment of generalized bullous morphea is difficult, and controlled studies are lacking. Options reported in the literature include potent topical steroids, anti-inflammatory agents, systemic steroids, hydroxychloroquine and other antimalarials, salazopyrin, disease-modifying agents such as cyclophosphamide, and psoralen ultraviolet A (PUVA); all these agents have variable efficacy.

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Presented by Joaquin Brieva, MD, Joan Guitart, MD, James Herrmann, MD and James Collyer, MD

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HISTORY OF PRESENT ILLNESS

The patient is a 27-year-old man who presented with an eight-year history of a persistent, erythematous, edematous, scaly plaque on his forehead. The lesion was not pruritic or painful, but it occasionally burned. He also noted another lesion under the right axilla as well as redness and scaling of the neck and upper chest that had been present for approximately the same period of time. Prior to the development of the forehead lesion, the patient had acne involving the affected area. Previous treatments include multiple topical medications (fluticasone, betamethasone valerate, clindamycin, benzoyl peroxide, tacrolimus, pimecrolimus, tretinoin), an intralesional steroid, and various anti-seborrheic shampoos. None of these agents resulted in significant improvement. He denied manipulating the lesion or any associated fevers, night sweats, weight loss, or malaise. A skin biopsy was performed of the forehead plaque that showed a dense dermal granulomatous reaction, and it was felt that the patient had a cutaneous granulomatous dermatitis of unknown etiology. He was started on an empiric course of oral minocycline 100mg twice daily and returned to clinic three months later noting minimal improvement. Subsequently, a second skin biopsy was taken from the right lateral chest.

PAST MEDICAL HISTORY

Appendectomy

MEDICATIONS

Cetaphil lotion and topical tacrolimus

PHYSICAL EXAM

On the central forehead there is a 10 cm, ill-defined, edematous, erythematous plaque with some scaling and inflammatory papules on the periphery. On the right lateral chest there is an ill-defined, erythematous, poikilodermatous plaque with fine scale. Similar poikilodermatous lesions are present on the neck and upper chest.

HISTOPATHOLOGY

DP 06-6432 (mid forehead): The specimen shows a dense dermal infiltrate composed primarily of lymphocytes and plasma cells with some multinucleated foreign body giant cells. The surrounding stroma shows some fibroplasia. Colloidal iron stain revealed mildly increased dermal mucin. Special stains for microorganisms were negative and polarizable material was not identified.

DP 06-10061 (right chest): There is a superficial band-like infiltrate with prominent epidermotropism. The lymphocytes are intermediate in size with hyperconvoluted nuclear detail. The papillary dermis shows reticular fibroplasia. The infiltrate is predominantly CD4 positive with a CD4:CD8 ration of 4:1. There is decreased expression of CD7. Colloidal iron stain revealed minimally increased dermal mucin. Fresh tissue is positive for clonal T-cell receptor rearrangement by PCR.

LABORATORY RESULTS

The following were negative or within normal limits:

Complete blood count with differential, thyroid stimulating hormone, free T4

The following were abnormal:

Alanine aminotransferase 71, HDL 33, LDL 145

DIAGNOSIS

Mycosis fungoides initially presenting as a rosacea-like granulomatous dermatitis

TREATMENT AND COURSE

The patient was started on hydrocortisone 2.5% cream daily to the forehead and triamcinolone 0.1% cream with Eucerin daily to the trunk lesions, PUVA with oral methoxsalen 50 mg three times weekly, oral bexarotene 75 mg three times weekly (recently increased to 150 mg daily Monday through Friday after follow-up visit), a low fat diet, omega 3 fatty acids, and atorvastatin 10 mg daily. On follow-up, he noted a minor decrease in the size of the plaque on his right lateral chest, but he also had worsening pruritus.

DISCUSSION

Cutaneous T-cell lymphoma (CTCL) is a neoplasm of T cells which usually first manifests on the skin. In general, CTCL is a chronic, slowly progressive disease with a long evolution. The various subtypes of CTCL are distinguished by a combination of both clinical features and histopathology. Mycosis fungoides (MF) represents the most common type of CTCL and accounts for nearly 50% of all primary cutaneous lymphomas. Early on, the diagnosis may be difficult to establish because of its varied, and often non-specific, clinical presentation. Furthermore the pathological findings of early lesions may lack the diagnostic features observed in well-developed or advanced disease. Clinical findings that may delay the diagnosis MF include the absence of typical patch or plaque lesions and the distribution of the lesions in photo-exposed areas such as the head, neck, and chest, rather than in the photo-protected areas more traditionally associated with MF.

This delay in diagnosis was seen with our patient who presented with a long history of a large, indurated, granulomatous-appearing forehead plaque that had been treated as acne vulgaris, rosacea, and a nonspecific dermatitis. The initial forehead biopsy showed a granulomatous reaction, and it was not until the second biopsy, which was taken from a separate site, that the diagnosis of MF was made. CTCL should be considered in any patient with a chronic, therapy-resistant, non-specific cutaneous eruption. In patients with non-specific histological findings, a high index of suspicion and multiple biopsies may eventually lead to a diagnosis of CTCL. Once the diagnosis of CTCL is established, accurate staging is essential both for proper treatment and prognosis.

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Presented by Joaquin Brieva, MD, Simon Yoo, MD and Victoria Nguyen, MD
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Patient A

HISTORY OF PRESENT ILLNESS

The patient is a 60-year-old man with end stage renal disease on hemodialysis who was hospitalized six months ago for chest pain. Dermatology was consulted on 4/18/06 for a two-week history of bilateral lower extremity swelling, pain, redness, and firmness. Lower extremity dopplers were negative for deep venous thrombosis. The patient has no history of gadolinium exposure.

PAST MEDICAL HISTORY

Renal failure (started dialysis 5/05), multiple myeloma kappa light chain in remission (diagnosed in 1995 at Stage IIB), neuropathic pain secondary to bortezomib, benign prostatic hypertrophy, hyperlipidemia, hypertension, coronary artery disease status post stent, reflux disease, osteoarthritis, gout, left arm fracture

MEDICATIONS

Furosemide, calcitriol, tamsulosin, isosorbide dinitrate, clopidogrel, amlodipine, lansoprazole, finasteride, atorvastatin, acyclovir, erythropoietin

ALLERGIES

No known drug allergies

FAMILY HISTORY

Mother died of "bone cancer"

SOCIAL HISTORY

The patient is married and was a former salesman, now on disability. Patient has one son and two daughters. He is from Croatia and has been in the United States for 40 years. Patient has a remote history of tobacco and quit 30 years ago. No alcohol.

PHYSICAL EXAM

On the bilateral legs there is brawny induration with violaceous discoloration associated with sclerodermoid changes, a burning sensation, and scaling.

HISTOPATHOLOGY

DP 06-4705 (left thigh): The dermis shows an increased number of fibroblast extending into the deep subcutaneous septate. There is also some evidence of mucin deposits with wavy fibroblast and clear spaces. CD34 shows an increased expression within the fibromyxoid areas.

LABORATORY RESULTS

The following were abnormal:

Blood urea nitrogen 57, creatinine 5.8

Patient B

HISTORY OF PRESENT ILLNESS

The patient is a 63-year-old man with kidney failure requiring dialysis and two renal transplants who was referred to dermatology by his transplant nephrologist on August 4, 2006 for a six-week history of thickening of the bilateral upper and lower extremities and

trunk. The patient's first renal transplant was a cadaveric transplant in February of 1990 after nine months of dialysis for renal failure secondary to hypertension. This transplant failed secondary to cyclosporine toxicity by July 2006. Three weeks (July 14, 2006) prior to presentation, the patient had a second living related kidney transplant. Of note, the patient has had MRI with gadolinium on July 30, 2006.

PAST MEDICAL HISTORY

Renal transplants in February 1990 and July 2006, hypertension, hyperlipidemia, chronic atrial fibrillation, diabetes mellitus type II, myocardial infarction status post three stents, right hip replacement, cataract with lens replacement, peripheral vascular disease status post amputation of right toes, and peptic ulcer

MEDICATIONS

Sirolimus, tacrolimus, metoprolol succinate, sulfamethoxazole and trimethoprim, clopidogrel, fenofibrate, prednisone, and warfarin

ALLERGIES

Heparin

FAMILY HISTORY

Noncontributory

SOCIAL HISTORY

The patient has a 15-year tobacco history, but quit 25 years ago.

PHYSICAL EXAM

On the bilateral upper and lower extremities and trunk, there are firm, sclerotic diffuse plaques with patchy hyperpigmentation and without discharge or erosion.

HISTOPATHOLOGY

DP 06-9555 (right upper thigh): Square shaped punch of dermis with dense fibrosis of dermal collagen with numerous stellate fibroblasts. Pools of mucin are also identified. The changes are seen extending into the subcutaneous septa. Immunohistochemical staining for CD34 was weakly positive within deep fibroblasts. Colloidal iron staining showed intense deep dermal and subcutaneous deposits.

LABORATORY RESULTS

The following were negative or within normal limits:

Blood urea nitrogen 20, creatinine 1.5

DIAGNOSIS

Nephrogenic systemic fibrosis (formerly known as nephrogenic fibrosing dermopathy)

TREATMENT AND COURSE

Patient A is currently being treated with topical calcipotriene ointment and halobetasol propionate ointment twice a day. The patient was instructed to collect data from his dialysis machine regarding type of membrane material used and dialysate (brand, type, etc.).

Patient B is currently not undergoing any treatment for this condition.

DISCUSSION

Nephrogenic systemic fibrosis is a newly described fibrosing condition. It was first described by Cowper *et al* in 2001 as a scleromyxedema-like illness associated with renal failure. This condition has been seen in patients on hemodialysis and peritoneal dialysis, as well as in patients who have not been dialyzed but have acute renal failure. The extent of renal failure or etiologies of renal failure do not seem to correlate with extent of disease.

Clinically, this condition affects children and adults who present with recent hardening and thickening of skin. It involves brawny or erythematous, sclerotic, indurated, or edematous plaques with or without peau d'orange-like changes on the extremities and trunk. Yellow scleral plaques have been observed. Symptoms include pruritus or burning. Contractures and limited range of motion can occur, which can limit some patients to being wheelchair-bound. Unlike scleromyxedema, nephrogenic systemic fibrosis spares the face and does not involve paraproteinemia. However, some patients have circulating antiphospholipid antibodies. Extensive soft tissue calcification and systemic involvement are rare. Systemic involvement includes calcification and fibrosis of the diaphragm, lungs, myocardium, skeletal muscles, renal tubule and rete testes. This has been described as nephrogenic systemic fibrosis.

The etiology of nephrogenic systemic fibrosis is still unclear. Several hypotheses include CD34 and procollagen positive circulating fibrocytes, gadolinium and metabolic acidosis, antiphospholipid antibodies, recombinant erythropoietin or cyclosporine or azathioprine, angiotensin converting enzyme inhibitors, hepatitis C, environmental agent in dialysis tubing, and CD68 positive profibrotic growth factor TGF-Beta.

Histologically, early lesions show increased interstitial fibrocytes in the dermis and fibrous trabeculae in the subcutis. Later, lesions show increased fibrous trabeculae, increased elastic fibers, thickened fibrous septa of the panniculus, thick collagen bundles, and variable mucin deposition. Immunohistochemical staining is positive for CD34 and procollagen in dermal spindle cells, in contrast to morphea.

This condition is chronic and progressive. Correction of renal failure can improve skin manifestations; however, most persist despite correction. There is no standard therapy as of yet. Photodynamic therapy with light-emitting diodes post topical methyl aminolevulinate (applied for three hours under occlusion) and thalidomide may be promising. Retinoids, steroids, vitamin D analogs, and immunosuppressive therapy are not effective. Inconsistent responses have been seen with plasmapheresis, PUVA, photopheresis, cyclosporine, cyclophosphamide, intralesional steroids, intralesional interferon-alpha, and intravenous immunoglobulins.

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Presented by Joan Guitart, MD and Susan Lai, MD
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HISTORY OF PRESENT ILLNESS

The patient is a 57-year-old man who presented with waxing and waning erythematous lesions on his arms and an enlarging verrucous lesion on his left knee for the previous five to six years. He does not have a primary care physician and never had these lesions evaluated. Approximately one year ago he poured hot lime juice on the left knee lesion and since then, he developed worsening ulceration of the area. He had not sought any medical attention for these complaints prior to coming to our clinic. He denied any fever, chills, night sweats, weight loss or malaise.

MEDICATIONS

Acetaminophen

ALLERGIES

No known drug allergies

FAMILY HISTORY

Mother with lung and liver cancer.

PHYSICAL EXAM

On the bilateral forearms there are thin pink patches in an annular configuration. On his left medial distal thigh there is a 10 cm x 6 cm ulcer with heaped up borders and necrotic edges. On the left medial knee there is a 5 cm x 5 cm verrucous plaque with multiple 1-2 cm similar satellite lesions with extensive surrounding erythema and induration. There is no palpable inguinal, axillary, or cervical lymphadenopathy.

HISTOPATHOLOGY

DP 06-7512 (left leg): The epidermis is markedly corrugated with prominent verrucous projections. There is a dense dermal infiltrate composed of large pleomorphic lymphocytes with extensive epidermotropism and necrosis. The infiltrate is predominantly CD8+, while the large cells are negative for CD30 and CD4. DPAS was negative for fungi.

DP 06-7512 (left arm): There is a superficial band-like lymphoid infiltrate with prominent epidermotropism. The lymphocytes are intermediate to large in size with hyperconvoluted nuclear detail and the papillary dermis shows reticular fibroplasia. The immunophenotype of the large cells is CD8+ and CD30+ and the CD4:CD8 ratio is 2:1.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Basic metabolic panel, neutrophils, lymphocytes, eosinophils, basophils, alanine aminotransferase, alkaline phosphatase, bilirubin, platelets

The following were abnormal:

White cell count 13.3, absolute monocyte count 1.8, albumin 3.4, quantitative IgA 548, serum alpha1 0.3, serum alpha2 1.0; wound culture: rare *Staphylococcus aureus* and Lancefield group B beta-hemolytic *Streptococcus*; CT scan of the abdomen and pelvis with contrast: Minimally enlarged lymph nodes in the left groin and a borderline lymph node in the left external iliac nodal region, possibly reactive, with no evidence of pathologic adenopathy in the chest or abdomen.

DIAGNOSIS

Pagetoid reticulosis (cutaneous T-cell lymphoma, CD8+ phenotype)

TREATMENT AND COURSE

The patient received localized external beam radiation therapy to the left knee and one month later there was reduced ulceration and verrucous hyperkeratosis. He was also able to ambulate better after the radiation treatment. The patient is scheduled for follow-up with Radiation Oncology for possible further localized radiation treatment. In addition, topical nitrogen mustard may be added for treatment of his arms.

DISCUSSION

Pagetoid reticulosis, also known as Worringer-Kolopp disease and localized epidermotropic reticulosis, is a rare cutaneous T-cell lymphoma (CTCL) representing about 0.6% of all CTCL cases and affecting mainly adult men. Lesions of pagetoid reticulosis often have a corrugated appearance with a keratotic rim and usually enlarge very slowly, following a benign course. However, in 1931, Ketron and Goodman first reported a case with disseminated eruption and histopathological findings similar to those of Worringer-Kolopp disease. This disseminated variant, or Ketron-Goodman disease, carries a worse prognosis than the classical, localized disease. Ketron-Goodman may progress to systemic lymphoma, in some cases leading to significant morbidity and death. At present, the World Health Organization and European Organization for Research and Treatment of Cancer classification systems consider pagetoid reticulosis to be an indolent form of primary cutaneous T-cell lymphoma, which should be differentiated from the disseminated entity, Ketron-Goodman disease.

Histologically the condition is characterized by an intense epidermotropic infiltrate of large and atypical lymphoid cells exhibiting a pagetoid pattern. Immunohistochemical staining of the atypical lymphoid cells can demonstrate a heterogeneous T-cell phenotype; most cases are CD4-/CD8+, but a few are CD4-/CD8-. CD30 and Ki-67 positivity is often noted. Genotypic analysis may reveal T-cell receptor gene rearrangements (γ and/or β), indicating a clonal proliferation.

Our patient had a unique presentation in that his lesions were verrucous and ulcerative resembling blastomycosis. Pagetoid reticulosis usually presents with a solitary scaly erythematous patch or plaque on the extremity, and generally does not ulcerate. Despite the clinical severity of our patient's lesions, the prognosis of localized pagetoid reticulosis is good. Therapeutically, local excision and radiation therapy have been curative in most cases. Oral and topical PUVA have also proved effective. There is one report of pagetoid reticulosis treated successfully with topical 5-aminolaevulinic acid photodynamic therapy with clinical and histological clearance maintained at one year.

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Presented by Anthony J. Mancini, MD and Leslie P. Lawley, MD
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HISTORY OF PRESENT ILLNESS

The patient is a six-month-old boy who developed eczema and severe seborrheic dermatitis at the age of one month. He presented to our clinic at three months age with persistent, severe dermatitis and intertrigo despite appropriate therapy with topical corticosteroids, antifungals, emollients, and oral antibiotics.

PAST MEDICAL HISTORY

Delivered by elective C-section at 39 weeks estimated gestational age, with no complications in pregnancy or delivery; oral thrush noted one week prior to presentation

MEDICATIONS

Oral nystatin, cephalexin, oxiconazole nitrate cream, hydrocortisone 2.5% cream, and Cetaphil lotion

FAMILY HISTORY

Atopy. The patient has 4-year-old twin sisters who are both healthy.

PHYSICAL EXAMINATION

There is mild frontal bossing and a pinched nose. The scalp shows complete alopecia with erythema and greasy yellow scale. The neck, axilla, inguinal folds, scrotum, and perianal areas show erythema and erosive patches. Scattered over the trunk and extremities are multiple pinpoint erythematous macules and papules. The oral mucosa is clear. No petechiae, purpura, or lymphadenopathy is noted on exam.

HISTOPATHOLOGY

DP 06-343 (left posterior thigh): Interface and spongiotic dermatitis with necrotic keratinocytes consistent with GVHD and possible superimposed eczematous process.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Complete metabolic panel, mitogen assay panel, reduction of nitro-blue tetrazolium, and $\beta 2$ -leukocyte integrin expression

The following were abnormal:

White blood cell count 22.7; platelets 597, decreased levels of IgG, IgA, and IgM, absent tetanus titer; Peripheral blood smear: mild leukocytosis with absolute eosinophilia, mild increase in platelets with normal granulation, and mild polychromasia; Flow cytometry: increased absolute lymphocytes with elevated CD4 and decreased CD8 cells and significantly increased HLA-DR expression

DIAGNOSTIC COURSE

The patient was referred to our immunology consultant with the presumptive diagnosis of immunodeficiency and a concern about potential associated ectodermal dystrophy and NF- κ B essential modulator (NEMO) mutation. Severe combined immunodeficiency (SCID) was felt to be unlikely, as lab results revealed that cellular immunity was present. However, the immunologist raised the concern for maternal T-cell engraftment with cutaneous graft versus host disease, as would be seen with a SCID variant. Over the next

two months the patient continued to have persistent skin dermatitis, including diffuse erythroderma, intertrigo and seborrhea. Skin biopsy was performed and revealed changes consistent with graft-versus-host disease (GVHD) (see above). Maternal variable nucleotide tandem repeat studies, however, were negative for maternal engraftment. Genetic testing for NEMO mutation was positive, revealing a cytosine insertion in the zinc finger domain of exon 10.

DIAGNOSIS

Ectodermal dysplasia with immunodeficiency, secondary to NEMO mutation. Interestingly, his mother (on further history) has a history of incontinentia pigmenti.

TREATMENT AND COURSE

The patient was initially treated with intravenous immunoglobulin (IVIg) infusions, cyclosporine A, prednisone, and antibiotics. Subsequently he received an allogeneic stem cell transplantation from his HLA-matched sister. At first he revealed engraftment of donor cells and clearing of his skin manifestations. However, over the next few months the VNTR counts waned. He presented with recurrence of erythroderma, and repeat biopsy again showed interface and spongiotic dermatitis with necrotic keratinocytes. Although his skin has been difficult to manage, the patient has not developed a serious systemic infection to date.

DISCUSSION

X-linked anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID) is a rare genodermatosis caused by a hypomorphic mutation in the NEMO gene. NEMO is an important member of the kinase that releases Inhibitor of NF κ B (IKB) from NF- κ B so that NF- κ B may translocate to the nucleus and initiate transcription of genes involved in immunity, inflammation, apoptosis, adhesion, and cell growth. Patients with EDA-ID present with findings of ectodermal dysplasia (hypotrichosis, hypohidrosis, heat intolerance, and hypodontia) and variable immunodeficiency with recurrent bacterial, mycobacterial, and/or viral infections. Aside from the features of ED, cutaneous abnormalities described include dry, pale, wrinkled, and/or hyperpigmented skin. Our patient presented with persistent, severe eczema, seborrhea, and intertrigo that progressed to erythroderma as seen in cases of SCID or Omenn syndrome. Skin biopsy was consistent with GVHD; however maternal engraftment studies were negative. This GVHD-like skin presentation may be explained by autoreactive T-lymphocytes or keratinocyte apoptosis related to the NEMO defect as seen in incontinentia pigmenti. Patients are treated supportively for their ED symptoms including application of skin cooling techniques and proper dental care. The immunodeficiency may be treated with IVIg, interleukins, interferons, and antimicrobial agents. A few patients (including ours) have received hematopoietic stem cell transplantation in an effort to reconstitute the immune system. Long term outcome of stem cell transplant is yet to be determined.

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Presented by Sarah Chamlin, MD and Diana Leu, MD
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HISTORY OF PRESENT ILLNESS

The patient is a newborn girl born at 41+ weeks gestation with multiple congenital anomalies including hypoplastic right ventricle, large ventricular septal defect, atrial septal defect, patent ductus arteriosus, and tricuspid stenosis who was noted to have atrophic lesions on her temples and was also being evaluated by Ophthalmology for possible conjunctivitis.

PAST MEDICAL HISTORY

Born following normal spontaneous vaginal delivery at 41+ weeks gestation with multiple congenital cardiac anomalies; no complications noted during pregnancy

MEDICATIONS

Ranitidine and metoclopramide

ALLERGIES

No known drug allergies

FAMILY HISTORY

Her parents are from Yemen with no history of consanguinity. Mother denied use of any tobacco, medications, or illicit drugs. Prenatal ultrasounds were normal as per mother. Paternal niece was born without a forearm on left upper extremity and maternal cousin had an unknown congenital heart defect. Maternal uncle's wife with three miscarriages (cause unknown).

PHYSICAL EXAM

Alert and active infant with low set ears, bulbous and fleshy nasal tip, full upper lip, edema of eyelids, multiple rows of upper eyelashes and inverted V-shaped eyebrows. Multiple bilateral atrophic macules are present at the temples. There is also an accessory nipple and a V shaped cleft between the labia majora. The nails and hair are normal.

HISTOPATHOLOGY

None

DIAGNOSIS

Setleis syndrome

TREATMENT AND COURSE

Genetic testing revealed a normal female karyotype and absence of a 22q deletion. The patient is planned for cardiac surgery when she is approximately six months of age.

DISCUSSION

Setleis syndrome was first described by Setleis in 1963. He described a congenital facial ectodermal dysplasia in members of three unrelated families from Puerto Rico. The findings in Setleis syndrome include temporal skin depressions described as "forceps marks," absent or multiple rows of eyelashes, upslanting eyebrows, periorbital puffiness, large lips with down turned corners, and hypo- or hyperpigmentation of the skin. Other anomalies have also been described, including an imperforate anus, megaureter,

supernumerary nipples, and bifid scrotum. It is a rare syndrome with approximately 25 cases described in the literature. Setleis syndrome was initially thought to be an autosomal recessive condition found in a single ethnic group. However, additional case reports point towards an autosomal dominant inheritance that occurs in many ethnic groups including Puerto Rican, German, Japanese, Arabic, and Samoan. Patients with Setleis syndrome were thought to have normal growth and development, but several case reports have also documented patients with learning disabilities.

The pathogenesis of Setleis syndrome is unknown. Matsumoto et al propose that the characteristic facies was secondary to an embryological disorder occurring in the frontonasal process and the first branchial arch. The "forceps marks" are located at the junction between these two embryologic processes. They propose that the findings in Setleis syndrome are secondary to insufficient migration of neural crest cells during embryogenesis. Some sources consider Setleis syndrome and focal facial dermal dysplasia to be the same entity. The latter condition is characterized by bitemporal cutis aplasia, similar to Setleis syndrome, but without the other facial abnormalities. Given their similarities, the two conditions may represent one disease with a spectrum of clinical features secondary to variable penetrance and expressivity. Our patient has many of the features found in Setleis syndrome. In addition to the findings described in the original report, our patient also has an accessory nipple, as described in later case reports as well as many cardiac anomalies, which have not been previously reported.

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Presented by Amy Paller, MD and Aimee Hawrot, MD
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HISTORY OF PRESENT ILLNESS

The patient is a 23-year-old man who has been diagnosed with Costello syndrome and was followed during his childhood at the Division of Dermatology at Children's Memorial Hospital. At that time he had numerous filiform papillomata that were not terribly bothersome. He was not seen for several years, but presented again in April 2006 with marked progression of his warty lesions, particularly on the plantar surfaces bilaterally and on his face. He had been treated previously with cryosurgery, topical retinoids and topical imiquimod without significant improvement. Previous biopsy of the verrucous plaque on the plantar aspect of the right foot was considered consistent with human papilloma virus (HPV) infection.

PAST MEDICAL HISTORY

Costello syndrome, with significant scoliosis and hypertrophic cardiomyopathy; he has had multiple surgeries for bony abnormalities

MEDICATIONS

Verapamil, stool softener, pantoprazole, and imiquimod cream

ALLERGIES

No known drug allergies

FAMILY HISTORY

Noncontributory, no affected family members

SOCIAL HISTORY

Unremarkable; the patient lives at home with his family

PHYSICAL EXAM

Characteristic features include broad nose, thick lips and loose elastic skin. On the right cheek, there is a 3 cm x 4 cm hyperkeratotic plaque, with several scattered hyperkeratotic papules at bilateral temporal areas, right preauricular cheek, and right conchal bowl. He also has multiple 1-4 cm hyperkeratotic plaques on the plantar surfaces of the feet bilaterally.

HISTOPATHOLOGY

J 05-9989 (foot): Superficial shave biopsies of a papillary lesion show acanthosis with hyperkeratosis and focal parakeratosis. There is scattered coarse keratohyalin and vacuolization within the granular cell region, compatible with the clinical history of mosaic verrucae. No atypical keratinocytes are seen.

DIAGNOSIS

Costello syndrome

TREATMENT AND COURSE

After sensitization with squaric acid dibutyl ester, the patient initiated immunotherapy with both 0.6% squaric acid to the feet and injections of *Candida* antigen 1:100 to the cheek and ear. After two months, improvement was noted on the cheek and ear, but

not on the soles. *Candida* injections were extended to the feet and the squaric acid dibutyl ester concentration was increased to 1.2%. By the time of the Chicago Dermatological Society meeting, he will have had four injections to the facial plaque and three to the foot.

DISCUSSION

Costello syndrome (OMIM 218040) was first described in the 1970s, and classically has been grouped with similar rare genetic syndromes involving the Ras/mitogen-activated protein kinase (MAPK) pathway. More recently, the genetic mutation in Costello syndrome has been identified specifically as *HRAS*, in most cases de novo, in contrast to Noonan syndrome, which involves *PTPN11*, and the cardio-facio-cutaneous syndrome, which involves *KRAS*, *BRAF*, *MEK1* and *MEK2*. Costello syndrome classically manifests with multiple congenital anomalies, including characteristic facies, distinctive hand posture, cardiac abnormalities, ventricular dilatation and Chiari malformation, short stature and developmental delay with gregarious nature. Feeding difficulty and failure to thrive may also occur, and affected pregnancies tend to show polyhydramnios and large birth weights. Cutaneous features include redundant, thickened, velvety, sometimes olive-colored skin, which is most prominent at the palms and soles. During early childhood and adolescence, about half of patients develop papillomata, particularly at the face and nasolabial folds, as well as on other moist body surfaces. There is increased risk of malignancy, including rhabdomyosarcoma, neuroblastoma, and bladder carcinoma, among others. Delayed puberty, hypogonadism, osteoporosis, benign breast disease, and gastroesophageal reflux can also occur in affected individuals.

Our patient presented with a history of multiple warty plaques for many years duration, which were previously unresponsive to cryosurgery and topical therapies. Biopsy had confirmed these lesions to be consistent with verruca vulgaris, however, the etiology of such lesions in the presence of Costello syndrome is not well understood. Our approach thus far has consisted of immunotherapy, specifically with *Candida* injections and squaric acid, which has shown some improvement of his lesions. We present this case as a classic example of this rare genetic disorder and to highlight the recent discovery of its causative mutation. Neither the recalcitrant nature nor treatment of the associated papillomata has been well-described in the literature.

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Presented by Anthony J. Mancini, MD and Brandi Kenner-Bell, MD
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HISTORY OF PRESENT ILLNESS

The patient is a four-year-old girl who presented to the Children's Memorial Hospital Emergency Department (CMH ED) with a bullous skin eruption present for the prior six weeks. The eruption began as red, itchy bumps, initially diagnosed by a dermatologist as hives and then eczema. She was prescribed Eucerin cream and loratadine. However, the lesions persisted, and after about a week, the patient developed small blisters on the lower face, legs, arms, and trunk. The blisters gradually increased in number and size, so she presented to an outside emergency room and received one dose of oral prednisone. She was also referred back to her dermatologist, who subsequently performed biopsies from two sites. The mother was informed that the results of the biopsy were consistent with linear IgA disease, and she was referred to Dr. Mancini, with instructions to go to the CMH ED with any fever or "eye symptoms." No further treatment was given. The day before the patient presented to the CMH ED, she developed a temperature of 100° F, increasing number of lesions on the face, and increasing pain and discomfort, which prompted her to go to the ED. The patient had no other systemic signs or symptoms.

PAST MEDICAL HISTORY

Significant only for allergies to pears and pear juice

MEDICATIONS

Neomycin-bacitracin-polymyxin B ointment

ALLERGIES

No known drug allergies

PHYSICAL EXAM

On the thighs, legs, feet, arms, forearms, and trunk, there are numerous tense bullae were present, ranging from 5 mm to >4 cm. Several blisters on her trunk reveal a "string-of-beads" morphology with scant sero-sanguinous discharge. On the face, scalp, and trunk, there are crusted papules. Total body surface area of involvement is approximately 80%. No oral mucosal lesion and no lymphadenopathy is present.

HISTOPATHOLOGY

DP 06-04932 (left lower arm): Subepidermal blister with a superficial perivascular and interstitial infiltrate containing numerous neutrophils.

Direct immunofluorescence: Linear staining at the dermal-epidermal junction with IgA; negative for C3, IgM, and IgG.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:
Complete blood count with differential, G6PD level

DIAGNOSIS

Linear IgA bullous dermatosis (chronic bullous disease of childhood)

TREATMENT AND COURSE

In the CMH ED, the patient was started on prednisolone (1 mg/kg/day) and hydroxyzine. The patient was seen in clinic the following week and was advised to taper the prednisolone over three weeks. She was started on dapsone ~0.7 mg/kg/day daily, cephalexin for 7 days, topical bacitracin ointment for open areas, and acetaminophen with codeine as needed for pain. Within two weeks, the patient's skin improved dramatically. Approximately one month after initiation of dapsone, she began to develop some new blisters, and her dose was increased to ~1 mg/kg/day with improvement.

DISCUSSION

Linear IgA bullous dermatosis (LABD), also known as chronic bullous disease of childhood, is a rare, self-limited autoimmune subepidermal blistering disease. The clinical features include tense vesicles and bullae developing de novo or on an urticarial base. In childhood-onset disease, lesions are most prominent on the lower abdomen and perineum, and frequently occur in a configuration known as "cluster of jewels," where new lesions occur at the periphery of older blisters. The trunk, extremities, face, and mucous membranes may also be involved. The onset is generally during the preschool years (though cases in neonates have been reported), with an average of about 4 years before resolution. However, LABD can have relapses and remissions with continuation of the disease into adulthood.

Diagnosis of LABD in the research setting requires three criteria: (1) presence of a vesicular or bullous eruption, usually confined to the skin, but which may involve the mucous membranes; (2) presence of a subepidermal vesicle with a predominant neutrophilic infiltrate on histology; and (3) presence of basement membrane zone-specific IgA antibody deposited in a linear pattern in the absence of other immunoglobulins in direct immunofluorescence of perilesional skin. However, there have been several cases reported with deposition of IgG in a linear pattern along the basement membrane in addition to IgA. These cases pathologically represent an overlap of LABD and bullous pemphigoid and in general should be treated clinically in accordance with whichever antibody response predominates. There are likely multiple target antigens in LABD, but the major antigen is a 120 kDa-secreted protein portion of the BP180 antigen, formerly known as LAD1.

First-line therapy for LABD is dapsone, started at a dose of 0.5 mg/kg/day and gradually increased as tolerated, with close laboratory monitoring, up to a maintenance dose of 1 mg/kg/day. An alternative treatment is sulfapyridine with or without systemic steroids. Other reported treatments include erythromycin, dicloxacillin, and colchicine. Mycophenolate mofetil was reported to have excellent results in one patient with dapsone-resistant disease.

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Presented by Joaquin Brieva, MD and Ki-Young Suh, MD
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HISTORY OF PRESENT ILLNESS

The patient is a 58-year-old man with acute myelogenous leukemia who was admitted to the Oncology service for induction chemotherapy with cytarabine and daunorubicin. After approximately two weeks, he developed fevers. Blood cultures were negative, a transesophageal echocardiogram ruled out vegetations, and a CT examination of the sinuses was unremarkable. Shortly after the fevers began, he developed a purpuric eruption on his hands that rapidly progressed to involve most of his body surface area. At the same time, he also developed hemoptysis, and a CT examination of the chest revealed bilateral patchy consolidations. He soon developed hypoxemic respiratory distress and was transferred to the medical intensive care unit, where he required mechanical ventilation.

PAST MEDICAL HISTORY

Myelodysplastic syndrome/myeloproliferative disorder diagnosed in April 2006 with transformation to acute megakaryoblastic leukemia in June 2006, hyperlipidemia and hypertension

MEDICATIONS

Acyclovir, aztreonam, caspofungin, daptomycin, gentamicin, voriconazole, esomeprazole, felodipine, and filgrastim

ALLERGIES

Ceftazidime and vancomycin

PHYSICAL EXAM

Firm, edematous, erythematous to violaceous papules and papulonodules are distributed diffusely on the arms, trunk, and legs. The face, neck, and mucous membranes are spared. Many of the lesions have a pseudovesicular appearance, and a few have secondary ulceration from rupture of overlying bullae.

HISTOPATHOLOGY

DP 06-8735 (right anterior thigh): Slight spongiosis of the epidermis with occasional neutrophils. The dermis shows dense papillary edema with abundant diffusely scattered neutrophils.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Complete blood count; Bronchoscopy: Negative for bacterial and fungal growth and negative for atypical cells

The following were abnormal:

Neutrophils >70%

DIAGNOSIS

Bullous Sweet's syndrome with fatal neutrophilic alveolitis

TREATMENT AND COURSE

The patient was treated with methylprednisolone 1 mg/kg intravenously for 5 days, and then was switched to slow taper of oral methylprednisolone. The cutaneous lesions improved immediately. The patient's respiratory status also improved remarkably, and he was weaned off mechanical ventilatory support within ten days. However one week after weaning, he redeveloped hypoxemic respiratory distress, which progressed to acute respiratory distress syndrome. The family members and medical teams discussed the patient's poor prognosis, and a decision was made to withdraw life support. The patient passed away, and the family refused autopsy.

DISCUSSION

Sweet's syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by the following: 1) fever, 2) neutrophilia, 3) tender, erythematous, edematous papules, nodules, and plaques on the skin, and 4) an infiltrate consisting predominantly of neutrophils that are diffusely distributed in the upper dermis. It has been associated with malignancy, inflammatory bowel disease, medications (such as granulocyte colony-stimulating factor), upper respiratory tract or gastrointestinal tract infection, and pregnancy. An overwhelming proportion malignancy-associated Sweet's have hematologic disorders, most commonly acute myelogenous leukemia. In malignancy-associated Sweet's, the cutaneous lesions can be more severe and may develop vesicular, bullous, and ulcerative changes. Oral mucosal involvement is more common in this group. Also important to consider is that leukocytosis is often absent in malignancy-associated Sweet's syndrome. Extracutaneous involvement is seen in up to 50% of malignancy-associated cases. The muscles and kidneys are more commonly involved, but the eyes, lungs, and liver can also be affected. The course of cutaneous and extracutaneous Sweet's syndrome is usually parallel, such that they develop and respond to therapy simultaneously.

The therapeutic mainstay is systemic corticosteroids, which should be tapered slowly over 4-6 weeks. With tapering of the steroids, recurrence of lesions has been noted. In one patient reported to have Sweet's syndrome with pulmonary involvement, recurrence of infiltrates in the lungs was noted five separate times during the period in which the steroid was tapered. In malignancy-associated Sweet's, recurrence of lesions may also herald a recurrence of the malignancy itself. Accordingly, our patient's cutaneous lesions and pulmonary status improved promptly with steroid treatment. When the patient was weaned off the ventilator, he was on a slow taper of steroids. However he had a recurrence of respiratory distress requiring re-intubation for ventilatory support. This was assumed to be from neutrophilic alveolitis secondary to recurrent Sweet's syndrome; but because of the rapid decline in his status and his family's refusal for an autopsy, we could not determine with certainty the etiology of the second episode of his respiratory distress. This patient is being presented to discuss an atypical, bullous form of Sweet's syndrome with pulmonary involvement secondary to a hematologic malignancy.

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Presented by Joaquin Brieva, MD and Anjeli Krishnan, MD
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HISTORY OF PRESENT ILLNESS

The patient is a 34-year-old man with no significant past medical history who presented with an abrupt onset of a skin eruption that started on his face and spread to his trunk and upper and lower extremities. He denied groin lesions. The rash was not pruritic or painful. Approximately ten days prior to the rash developing, the patient developed a mild sore throat as well as pain with swallowing, with markedly diminished oral intake as a result. He has also had a 30-40 pound weight loss as well as profound weakness and fatigue during the previous six weeks. Shortly after the onset of his sore throat, a new white plaque developed on his tongue. He denied any constitutional symptoms, neurologic complaints, dysuria, or urinary discharge.

PAST MEDICAL HISTORY

Tonsillectomy and adenoidectomy

MEDICATIONS

Acetaminophen with codeine and ibuprofen elixir

ALLERGIES

No known drug allergies

SOCIAL HISTORY

The patient reported being in a monogamous relationship with his fiancée, with whom he had not had sexual intercourse, citing religious beliefs. He denied multiple female partners in the past or sex (oral or other) with prostitutes. He did report one episode of homosexual intercourse several years ago but stated he used barrier protection. He denied intravenous drug, tobacco, or alcohol use.

PHYSICAL EXAM

There are numerous round papules, plaques and nodules on the scalp, face, lips, extremities, trunk, and penis. The papules are firm and mildly erythematous, some with central umbilication, while some of the plaques and nodules are ulcerated and necrotic with thick, dark, lamellated, and adherent crusts. On the penis there are a few well-demarcated ulcers with heaped-up borders and a fibrinous base. There is an adherent white plaque covering the tongue. There are no pustules or vesicles present on the skin, and the palms and soles are clear.

HISTOPATHOLOGY

DP 06-4648 (left arm): There is a dense, band-like interface dermatitis present with plasma cells. The epidermis has a parakeratotic crust with serous exudate, neutrophils, nuclear debris, and hemorrhage. Numerous necrotic keratinocytes are noted. Anti-treponemal antibody staining is strongly positive and AFB, DPAS, gram-stain, human herpes virus 8, and mucicarmine stains are negative.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Tissue cultures for bacterial, atypical mycobacteria, and fungal growth

The following were abnormal:

RPR 1:8 dilution, VDRL positive, human immunodeficiency viral load 520,000, CD4 count 109

DIAGNOSIS

Noduloulcerative syphilis

TREATMENT AND COURSE

The patient received three weekly doses of intramuscular benzathine penicillin, 2.4 million units, with resolution of his lesions. Highly active anti-retroviral therapy was also initiated.

DISCUSSION

Noduloulcerative syphilis, also known in the literature as “malignant” syphilis, lues maligna, syphilis maligna praecox, or rupioid syphilis, is a rare variant of secondary syphilis. Less than 30 cases have been described in modern scientific literature, with the earliest case reported at Massachusetts General Hospital in 1821. The reason that only a small minority of patients with secondary syphilis develops this destructive variant is unknown, but there have been recent case reports describing noduloulcerative syphilis in the setting of human immunodeficiency virus (HIV). Long before the era of HIV, however, studies suggested altered cell-mediated immunity in patients with this form of syphilis.

Clinically, round or oval pleomorphic noduloulcerative lesions develop with a granulating base and a lamellated, brown-black rupioid crust. In fact, it is the rupioid (“stack of coins”) crust that makes this type of syphilis so distinctive. The surrounding skin is usually normal, occasionally exhibiting minimal erythema. These lesions are most often observed on the face, but can involve other parts of the body as well as the mucous membranes of the mouth and nose. Typically, the palms and soles are spared. Usually systemic symptoms are not pronounced, however hepatitis and spirochetal toxemia resulting in death have been reported in some patients with noduloulcerative syphilis. The differential diagnosis includes deep fungal infection (cryptococcus or histoplasma), penicilliosis, malignant pyoderma gangrenosum, verrucous sarcoidosis, leprosy, yaws, and mycosis fungoides.

A dense plasma cell infiltrate and endothelial cell swelling are observed under histologic examination. Necrosis of the epidermis can be seen, which corresponds to the rupioid crust. Vascular involvement with endarteritis and periarteritis is characteristic of all stages of syphilis. Recognizable spirochetes are often not seen, and their presence is not required for the diagnosis. RPR and VDRL will provide serological confirmation of syphilis. Knowledge of HIV status is critical, given that the two diseases often coexist.

Rapid response to treatment with intramuscular benzathine penicillin should be expected. Hence, the term “malignant” is a misnomer when describing this condition. Patients should have clinical and serological follow-up at 6 and 12 months after treatment. If there are persistent signs or symptoms or if titers do not decline appropriately, this may indicate treatment failure, which necessitates re-treatment. Again, these circumstances would be unusual, and response to therapy is the norm.

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HISTORY OF PRESENT ILLNESS

The patient is a 36-year-old woman with recently diagnosed acute myelogenous leukemia who presented with an eruption on her bilateral breasts and ears three days after completing induction chemotherapy with cytarabine and daunorubicin. Her hospital course was remarkable for neutropenic fevers with no clear source of infection and she was being treated empirically with numerous antimicrobials. The eruption began on both breasts, sparing the areolae and nipples, and spread to involve both ears and the upper extremities. She complained of a burning sensation and pruritus over the affected areas and denied any conjunctivitis or arthralgias.

PAST MEDICAL HISTORY

Acute myelogenous leukemia, M4 subtype

MEDICATIONS

Piperacillin-tazobactam, vancomycin, acyclovir, fluconazole, cetirizine, esomeprazole, norethindrone, oxycodone, lorazepam, zolpidem, prochlorperazin, acetaminophen, and docusate-senna

ALLERGIES

None

PHYSICAL EXAMINATION

On the bilateral breasts sparing the areolae and nipples, cheeks, neck, upper extremities, and periauricular area there are erythematous, indurated, papulo-nodules coalescing into plaques. Several lesions are mildly purpuric. No vesicles, pustules or surface change are noted.

HISTOPATHOLOGY

DP 05-9882 (right medial breast): There is a superficial and deep lymphocytic perivascular infiltrate. There is also a mid and deep peri-eccrine inflammatory infiltrate composed of numerous neutrophils, some of which are within the walls of the eccrine structures. Special stains for microorganisms were negative.

LABORATORY RESULTS

The following were negative or within normal limits:

Basic metabolic panel, direct and total bilirubin, alkaline phosphatase, aspartate aminotransferase

The following were abnormal:

White blood cell count 0.8, platelets 6, hemoglobin 8.1, hematocrit 23, albumin 2.5, alanine aminotransferase 72, total protein 5.4

DIAGNOSIS

Neutrophilic eccrine hidradenitis

TREATMENT AND COURSE

The patient was treated with cetirizine and the lesions resolved approximately ten days after her last dose of cytarabine. No recurrences were noted during her consolidation treatment with the same chemotherapeutic agents.

DISCUSSION

Neutrophilic eccrine hidradenitis (NEH) is an acute, self-limited eruption predominantly seen in patients undergoing chemotherapy for malignancy. First described by Harrist et al in 1982, NEH occurs most commonly with the use of cytarabine for the treatment of acute myelogenous leukemia. Other chemotherapeutic agents such as bleomycin, mitoxantrone and cyclophosphamide have also been implicated in the development of NEH. In addition it has been associated with the use of acetaminophen and anti-retroviral therapy as well as infections with *Serratia*, *Enterobacter*, and human immunodeficiency virus. NEH can have a variable clinical appearance but typically presents as edematous, erythematous papules and plaques on the head, neck and extremities occurring one to two weeks after institution of the offending agent. Purpura and vesico-pustules can also be observed. While most patients are asymptomatic, the lesions are occasionally pruritic or tender. The differential diagnosis includes Sweet's syndrome, pyoderma gangrenosum, leukemia cutis, and hypersensitivity reactions.

Histologically, NEH is characterized a variable infiltrate of neutrophils surrounding the eccrine glands. Necrosis of the eccrine secretory epithelium is often present. The pathogenesis of NEH is unknown but it has been hypothesized that it is the result of direct toxicity of chemotherapeutic agents on the eccrine units. This is supported by previous studies isolating these agents in sweat. However since NEH has been reported to occur in the absence of chemotherapy, the pathogenesis of this condition remains unclear. The course of NEH is generally self-limiting and lesions resolve without therapy in one to four weeks. Many patients, however, do experience a recurrence when re-treated with the offending agent. Symptomatic treatment with topical steroids, antihistamines and analgesics can be instituted and for severe cases, oral corticosteroids have been used.

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Presented by Anne Laumann, MBChB, MRCP (UK), Joaquin Brieva, MD, Joan Guitart, MD, and Victoria Nguyen, MD

HISTORY OF PRESENT ILLNESS

The patient is a 39-year-old Caucasian woman with a diverse presentation:

June 2004: She developed red-brown macules with no epidermal changes on her left posterior knee and hip. She was drinking 20 ounces of vodka and tonic every Saturday for six months. A diagnosis of a fixed drug eruption related to quinine was made, and she stopped drinking tonic water.

August 2005: She developed symptomatic speckled, petechial, pigmented and tan areas with red borders on the ankles.

October 2005: She complained of fatigue, arthralgias, mouth ulcers and a facial "butterfly" rash, chest and upper arm "sun-sensitive eruption" not seen by a dermatologist. She was started on oral quinacrine.

December 2005: She developed irregular bluish black areas of macular pigmentation behind her knees and on her ankles, as well as ill-defined edematous, erythematous, evanescent areas on her chest and upper arms. The patient did not have joint aches.

June 2006: Her skin was yellow, but her sclerae remained white. Spreading oval, violaceous, and papulosquamous plaques developed on her thighs, abdomen, axillae, and eyelids with indurated papules noted on her arms.

August 2006: She presented with fatigue, malaise, yellow skin and spreading oval thick violaceous scaly plaques on the lower abdomen, upper thighs, axillae, medial eyelids, buttocks and left breast.

PAST MEDICAL HISTORY

Allergic rhinitis

MEDICATIONS

Loratidine, mometasone nasal spray, oral norethindrone acetate and ethinyl estradiol, and quinacrine

ALLERGIES

Ofloxacin, sulfa drugs, ciprofloxacin, dicloxacillin, quinine, and penicillin

PHYSICAL EXAM

Yellow skin, white sclerae. There are oval shaped, lichenoid and violaceous plaques along the abdomen, medial thighs, buttocks, axillae, left breast, upper eyelids, and lower lip. On the left posterior knee, there is an oval, hyperpigmented macular patch. On her ankles, there are violaceous speckled, nonblanching patches.

HISTOPATHOLOGY

6/17/04 DP 04-5609 (left hip): Epidermis unremarkable. Superficial and deep, mild perivascular and deep interstitial lymphocytic infiltrate in the dermis. Colloidal iron stain

reveals no mucin deposition. The picture is consistent with a drug eruption, an annular erythema or possibly a proliferative lymphocytic disorder.

9/05 DP 05-8391 (medial left ankle): The epidermis shows mild spongiosis with exocytosis of lymphocytes into the lower portion. In the dermis there is a patchy perivascular and interstitial infiltrate of mononuclear cells with some variation in morphology but without cytologic atypia. The vessels show endothelial swelling and there is superficial extravasation of red blood cells. Although the vascular changes and extravasation are consistent with a pigmented purpuric dermatitis, the cytologic response raises the possibility of early mycosis fungoides.

12/8/05 DP 05-13151-II (behind left knee): Mild superficial perivascular lymphohistiocytic infiltrate with a few pigment laden macrophages.

12/8/05 DP 05-1315-I (right upper arm): Epidermis unremarkable. Dermis shows slight telangiectasiae with a minimal perivascular lymphohistiocytic infiltrate, consistent with urticaria.

6/2/006 DP 06-6760 (right lower abdomen): Epidermis with parakeratosis and hyperkeratosis. Superficial bandlike lymphohistiocytic infiltrate with prominent vacuolar changes along the basal cell layer. Papillary dermis shows some reticular hyperplasia. The lymphocytes are small to intermediate with some atypia and disarray. There are a few pigment-laden macrophages. Colloidal iron shows no evidence of dermal acid mucopolysaccharide deposits and a DPAS stain is negative for fungi.

Immunohistochemistry reveals CD4:CD8 ratio of 2:1. The changes are consistent with lupus erythematosus but mycosis fungoides cannot be completely excluded.

8/8/06 DP 06-9631 (right anterior thigh): Epidermis with focal parakeratosis, occasional apoptotic keratinocytes, and squamotization of the basal layer with an underlying lichenoid inflammatory infiltrate. Prominent eosinophils. The findings are consistent with a lichenoid drug eruption.

8/8/06 IF 06-08 (right anterior thigh): Negative for IgA, IgG1, IgG4, IgM, and C3 deposits. Minimal non-specific deposits of fibrinogen were seen at the dermal-epidermal junction.

8/8/06 Tissue T-cell Receptor Rearrangement by PCR is positive for T-cell clonality.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Complete blood count, dsDNA, U1 RNP/SNRNP IgG, SCL-70 IgG, Smith IgG, SS-A and SS-B IgG, cardiolipin IgG, IgM and IgA antibodies, C4, C3 and CH50, complete metabolic panel within normal limits except alanine aminotransferase

The following were abnormal:

Antinuclear antibody 75 (<7.5) (1:160) speckled pattern, alanine aminotransferase 62

DIAGNOSIS

Quinacrine-induced lichenoid drug eruption with positive T-cell clonality

Benign pigmented purpura

TREATMENT AND COURSE

The patient was prescribed fluocinonide 0.05% cream for the trunk and legs and pimecrolimus 1% cream for the eyelids and axillae on 8/8/06. She was instructed to stop quinacrine on 8/16/06. On follow-up on 8/22/06, she reported no improvement of lesions. On follow-up on 10/2/06, she reported improvement with flattening and less scale. We plan to follow-up with the patient 3 months after stopping quinacrine.

DISCUSSION

Lichenoid reactions can be associated with multiple medications including antimalarials, antimicrobials, antihypertensives, antidepressants, anti-anxiety drugs, anti-psychotics, anticonvulsants, diuretics, hypoglycemic agents, metals such as gold salts, nonsteroidal anti-inflammatory drugs, and penicillamine. Antimalarials include quinine (a drug made from the bark of the cinchona tree), quinacrine hydrochloride (synthetic quinine), hydroxychloroquine, and quinidine. Lichenoid reactions can be generalized or more commonly develop on photodistributed areas (lichenoid photoeruption). The pathogenesis is speculative. One theory is that CD4+ T-cells are activated after recognizing the drug antigen and release cytokines such as IFN-gamma and TNF, which cause epidermal injury. Often, discontinuation of the offending drug results in slow resolution with postinflammatory pigmentation.

Positive T-cell clonality has been described in multiple benign conditions, including adverse reactions to drugs, pityriasis lichenoides et varioliformis acuta, pityriasis lichenoides chronica, lichen planus, lichen sclerosus et atrophicus, and lichenoid purpura. It is important to recognize that clonality is not synonymous with malignancy. However, there is controversy as to whether some of these conditions may progress to cutaneous T-cell lymphoma. In addition, atypical lymphoid infiltrates, some of which are mycosis fungoides-like, have been described in drug eruptions consisting of erythematous plaques and infiltrative papules with resolution within one to thirty-two weeks of discontinuation of the offending agent.

Of note, our patient was initially diagnosed with a fixed drug eruption secondary to quinine. Despite this, quinacrine (synthetic quinine) was started (not by a dermatologist) for possible lupus. What is remarkable about our patient's presentation is that all the biopsies of each separate condition (fixed drug eruption, possible lupus, benign pigmented purpura, and the current drug-induced lichenoid eruption) show lymphoid reactions. Considering the clinical course and histopathology studies together, we believe that our patient has a drug-induced lichenoid eruption with positive T-cell clonality. Also, her yellow skin noted on exam is probably related to quinacrine, as was her elevated alanine aminotransferase, which has since normalized.

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Presented by Joan Guitart, MD and Ana Ciurea, MD
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HISTORY OF PRESENT ILLNESS

The patient is an 85-year-old woman who presented with a one-year history of asymptomatic bruise-like lesion on the abdomen and thighs in the absence of trauma. There has been gradual increase in size of the isolated lesions and new lesions have appeared on the extremities. She denied fever, chills, malaise, weight loss, decreased appetite or weakness.

PAST MEDICAL HISTORY

Tricuspid valve disease, pulmonary hypertension, hypertension, total abdominal hysterectomy and bilateral salpingo-oophorectomy, and left hip replacement

MEDICATIONS

Metoprolol, furosemide, simvastatin, and potassium supplement

ALLERGIES

Angiotensin-converting enzyme inhibitors

PHYSICAL EXAM

On the abdomen and thighs there are multiple, violaceous, annular 1-4 cm patches and plaques with central clearing. No hepatosplenomegaly or lymphadenopathy are appreciated.

HISTOPATHOLOGY

DP 06-10630 (right abdomen): Intravascular proliferation of large and atypical lymphocytes with pleomorphic features. Nuclear debris and fibrin thrombi are noted. The dermis shows a variable mostly perivascular lymphohistiocytic infiltrate. The malignant cells are strongly positive for CD20 and MUM-1 and negative for AE1/3, CD5 and CD3.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Complete blood count, comprehensive metabolic panel, lactate dehydrogenase, lipid panel, prothrombin time, partial thromboplastin time, International normalized ratio, CT chest, abdomen and pelvis

The following were abnormal:

Peripheral blood flow cytometry immunophenotyping: Abnormal B cell population (CD19+, CD10-, CD5-, CD20+, and CD52+)

DIAGNOSIS

Intravascular B-cell lymphoma, large cell type

TREATMENT AND COURSE

The patient will be followed closely for progression of disease. She remains asymptomatic and she has undergone no further work-up or treatment except regular physical exams. If therapy is required, most likely a single-agent (rituximab) would be appropriate.

DISCUSSION

Intravascular lymphoma (IVL) is a rare subtype of extranodal diffuse large B-cell lymphoma with a distinct presentation. The disease was first reported in the literature in 1959 by Pflieger and was described as "angioendotheliomatosis proliferans systemisata". It is characterized by the proliferation of clonal lymphocytes within small blood vessels with relative sparing of the surrounding tissue and absence of lymphoma cells in the lymph nodes and reticuloendothelial system. It had been described in patients with a wide range of ages and more often in the Asian population. There are several instances of IVL arising in the setting of diffuse large B-cell lymphoma and follicular lymphoma.

The predilection of the tumor cells for capillary endothelium is likely related to the expression of molecules on the surface of lymphocytes that allows for preferential binding within the vascular channel. Aberrant expression of CD11a and CD49d on the neoplastic cells has been proposed as a possible mechanism because these adhesion molecules enable tumor cells to home to CD54 (CD11a ligand) and CD106 (CD49d ligand), which are expressed on endothelial cell surfaces. Histology demonstrates the appearance of large malignant lymphocytes filling small vascular lumina. The classic immunophenotype of the malignant lymphocytes in IVL is B-cell-associated antigen-positive CD19+, CD20+, CD22+, CD79a. Most recently, two cases of an IVL of the natural killer cell phenotype were reported. The clinical symptoms of the disease are dependent on the specific organ involvement, which most often includes the central nervous system and skin. Fever of unknown origin and hemophagocytic syndrome are discrete clinical presentations. The skin manifestations are heterogeneous; lesions can appear as macular or papular eruptions, nodules, plaques, tumors, hyperpigmented patches, palpable purpura, ulcers, and an infiltrative "peau d'orange" appearance. Although IVL is a clonal proliferation of lymphocytes, it is uncommon to find significant adenopathy, hepatosplenomegaly, or circulating cells in the peripheral blood. Anemia, elevated lactate dehydrogenase, and elevated erythrocyte sedimentation rate are the most common laboratory abnormalities seen in IVL. Thrombocytopenia and leukopenia are less commonly seen.

There are no randomized, controlled trials comparing treatments of IVL, which in most of the cases, is disseminated at the time of diagnosis and warrants treatment with systemic therapy. Most cases of IVL are associated with a poor prognosis and should be treated with an anthracycline-based chemotherapy regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with or without the addition of the monoclonal antibody rituximab (R-CHOP). Intra-thecal or high-dose systemic methotrexate can be used if there is evidence of the disease within the CSF. Autologous hematopoietic stem cell transplantation should be considered in young patients with good performance status.

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Presented by Mario Lacouture, MD and James Collyer, MD
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Patient A

HISTORY OF PRESENT ILLNESS

The patient is a 38-year-old woman with relapsed acute myelogenous leukemia (AML) who had recently been started on troxacitabine, a deoxycytidine analogue that is in clinical trials for treatment of AML and various solid tumors. On day four of treatment, she developed several discrete vesicles and erosions on her arms and left dorsal hand. Topical clobetasol 0.05% cream was applied twice daily to the affected areas. By day 10, her palms and soles became very painful, edematous and erythematous. Her neck, arms, ankles and groin were also involved with pinpoint erythematous macules.

PAST MEDICAL HISTORY

AML, status post failed induction therapy x 2

MEDICATIONS

Ciprofloxacin, voriconazole, and acyclovir

ALLERGIES

Codeine, azithromycin, lorazepam, and sulfamethoxazole/trimethoprim

PHYSICAL EXAM

On the bilateral palms and soles there is diffuse erythema and tenderness with moderate edema. On the left dorsal hand there are three discrete, tense vesicles on minimally erythematous bases. Several, discrete, erythematous, 2-6 mm erosions with crust are noted on the bilateral forearms. The oral mucosa and conjunctiva are normal appearing.

HISTOPATHOLOGY

DP 06-9133 (left dorsal hand): There are multiple apoptotic keratinocytes at various levels of the epidermis. There is spongiosis most prominent around acrosyringium and syringosquamous metaplasia of the eccrine ducts. The dermis has prominent edema and there is a subepidermal separation.

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

Blood, urine, cerebrospinal and rectal cultures negative for bacterial and fungal growth.

The following were abnormal:

White blood cell count 0.7, hemoglobin 9.5, platelets 17, neutrophils 1%, lymphocytes 59 blasts 95% , D-dimer >4.0, alanine aminotransferase 220, aspartate aminotransferase 195 , LDH 495; Bone marrow biopsy: Markedly hypocellular bone marrow without definitive evidence of acute leukemia, status post chemotherapy.

DIAGNOSIS

Palmar-plantar erythrodysesthesia syndrome (PPES)

TREATMENT AND COURSE

The patient was started on oral prednisone 25 mg daily with improvement in the level of tenderness of her palms and soles. An appropriate bone marrow transplant match was not found and she was referred to an outside hospital for a phase I trial.

Patient B

HISTORY OF PRESENT ILLNESS

The patient is a 61-year-old woman with a past medical history significant for metastatic colon cancer who developed erosions and diffuse erythema of her hands three weeks after commencing her second treatment cycle of capecitabine, an oral 5-fluorouracil analog. This spontaneously improved in the week following her treatment cycle. One week into her third cycle these symptoms recurred and became progressively worse, with severe erosions and pain involving her bilateral hands and feet. The patient did not inform her oncologist of the progression until after completing the treatment cycle.

PAST MEDICAL HISTORY

Metastatic colon cancer status post chemotherapy and external beam radiation

MEDICATIONS

Fentanyl, morphine, aspirin with extended-release dipyridamole, levothyroxine, zolpidem, and omeprazole

ALLERGIES

No known drug allergies

FAMILY HISTORY

Father with lung and unspecified head/neck cancer

SOCIAL HISTORY

Previous tobacco user and occasional alcohol use

PHYSICAL EXAM

On the bilateral palmar and plantar surfaces, there is a well demarcated, erythematous, erosive eruption with fissuring, bullae formation and hemorrhagic crusting. The plantar surfaces are more severely affected than palmar surfaces.

HISTOPATHOLOGY

None

LABORATORY AND STUDY RESULTS

The following were negative or within normal limits:

White blood cell count

The following were abnormal:

Hemoglobin 10.2, eosinophils 9%, albumin 1.8, carcinoantigen 19-9 2118.7, TSH 57.6;

Wound culture of plantar surface: Many methicillin-sensitive *Staphylococcus aureus*.

DIAGNOSIS

Palmar-plantar erythrodysesthesia syndrome (PPES)

TREATMENT AND COURSE

The patient was started on oral pyridoxine (vitamin B6) 200 mg daily and cephalexin 500 mg every six hours. Her hands and feet were also treated with topical mupirocin and

covered with non-stick Telfa pads and Kerlix wrap. Once her infection had been adequately treated, triamcinolone 0.5% ointment was applied twice a day. A subsequent MRI of her neck demonstrated progressive metastatic colon cancer. Palliative care was initiated and she passed away shortly thereafter.

DISCUSSION

Palmar-plantar erythrodysesthesia syndrome (PPES), also known as acral erythema, hand-foot syndrome, and Burgdorf reaction, is a side effect of systemic chemotherapy and is characterized by dyesthesia of the palms and soles that evolves into a painful, symmetric, erythematous eruption. This is often followed by a desquamative phase on resolution. Erythema and swelling usually appear on the thenar and hypothenar eminences, lateral aspect of the fingers, and the pads of the distal phalanges. The hands are more often affected than the feet. PPES may also be accompanied by a mild erythema or a morbilliform eruption on the trunk, scalp, and extremities. According to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE), PPES is graded on three levels of severity (Table 1).

The chemotherapeutic agents most frequently implicated are doxorubicin, cytarabine, capecitabine and fluorouracil. Recently PPES has also been reported in phase I and II clinical trials of troxacitabine, a novel L-nucleoside analog. The etiology of PPES is currently unknown, but the fact that this condition is usually limited to the palms and soles may be a clue to elucidating its pathogenesis. Temperature gradients, vascular anatomy, the existence of rapidly dividing epidermal cells, and a high concentration of eccrine glands are all characteristics of palmar and plantar skin and these unique properties may play a role in the pathogenesis of this condition. A direct toxic effect of chemotherapy is also likely to play a role in the development of PPES as histopathology often reveals a non-specific toxic reaction. PPES appears to be dose dependent on peak levels and total cumulative dose, as it occurs earlier and more severely after bolus infusions as compared with continuous low-dose administration. Cessation of the causative agent usually results in resolution within one to two weeks and it may or may not recur with re-administration. The treatment of PPES is generally symptomatic, aimed at increasing tolerability to allow continuation of chemotherapy. Supportive treatment includes topical wound care, elevation, and pain control. Oral prednisone and pyridoxine has been reported to improve symptoms.

Although PPES is classically localized to the palms and soles, our patient on troxacitabine had prominent left dorsal hand involvement manifesting as discreet vesicles. Interestingly this same observation was also seen in another troxacitabine-treated patient at our hospital. Capecitabine-induced PPES classically presents within the first two cycles of administration. Our patient did not to inform her oncologist of the progression of symptoms until after therapy was completed. In general, patients on chemotherapy should be taught to recognize the symptoms of PPES.

Table 1

Grade	Presentation	Able to Perform Activities of Daily Living?
1	Mild skin changes (eg, erythema) without pain	Yes
2	Moderate skin changes (eg, desquamation, bleeding, edema, bullae) or pain	Yes, with some interference
3	Severe skin changes or ulcerative dermatitis	No

Adapted from the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

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