Chicago Dermatological Society

December 2014
Monthly Educational Conference

Program Information
Continuing Medical Education Certification
and
Case Presentations

Wednesday, December 3, 2014
Gleacher Conference Center

Conference Host:
Section of Dermatology
University of Chicago Hospitals
Chicago, Illinois

Program

Conference Location

Gleacher Conference Center
450 N. Cityfront Plaza Dr., Chicago

All meeting activities take place on the 6th Floor of the Gleacher Center.

8:30 a.m.	**Registration & Continental Breakfast with the exhibitors** *6th Floor Lobby*
9:00 a.m. - 10:00 a.m.	**University of Chicago Medenica Lecture** - Room 621 "Cutaneous Infections in Non-immunocompromised Hosts" *Wayne Grayson, MBChB, PhD, FCPath*
9:30 a.m. - 10:45 a.m.	**Clinical Rounds** Patient Viewing - *Rooms 600 & 602* Posters - *North Foyer* Slide Viewing - *Room 608*
11:00 a.m. - 12:00 p.m.	**General Session** - Room 621 LORINCZ LECTURE "Dermatopathology of HIV/AIDS: Lessons Learned" *Wayne Grayson, MBChB, PhD, FCPath*
12:00 p.m. - 12:30 p.m.	**Box Lunches & visit with exhibitors** *6th Floor*
12:30 p.m. - 12:45 p.m.	**CDS Business meeting** – Room 621
12:45 p.m. - 2:30 p.m.	**Case Discussions** – Room 621
2:30 p.m. - 2:45 p.m.	**MOC Self-Assessment Questions** – Room 621
2:45 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS monthly meeting... President's Conference and Annual Awards Luncheon
Wednesday, February 25, 2015 at the Stephens Convention Center in Rosemont

Illinois Dermatological Society Practice Management & Coding Workshop
Saturday, January 31, 2015; Stephens Convention Center in Rosemont

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

Guest Speaker

Delivering the Allen Lorincz Memorial Lecture and the University of Chicago Medenica Lecture

WAYNE GRAYSON MBCHB, PHD

Honorary Professor of Pathology; University of Witwatersrand; Johannesburg, South Africa

Dr. Wayne Grayson obtained his MBChB degree at the University of the Free State in 1989, and he earned his PhD at the University of the Witwatersrand in Johannesburg in 2001. In 1995 he obtained his FCPath (Anatomical) at the College of Medicine of South Africa.

Since 2008 Dr. Grayson has been Consultant Anatomical Pathologist and Dermatopathologist with AMPATH National Laboratories. He is an Honorary Associate Professor of Pathology, School of Pathology, at the University of the Witwatersrand. Professor Grayson has been the recipient of numerous awards, among them the SAIMR James Gear Prize for the most distinguished graduate in Pathology (1995) and the SAIMR Neville Proctor prize for the best anatomical Pathology research publication in 2009.

CME Financial Disclosure: Dr. Grayson has no significant financial relationships to disclose.

CONTINUING MEDICAL EDUCATION CREDITS

Chicago Dermatological Society

Presents

"2014 - 2015 Chicago Dermatological Society Monthly Meeting"

December 3, 2014 *Chicago, IL*

Please complete the CME claim form included in your meeting materials and return to the registration table before you leave the conference. A certificate of credit will be mailed to you following the meeting. Participants must attend entire session to receive full credit. Also, we ask that you complete the evaluation form attached to the claim form and return to the registration table. The information collected as part of this process represents an important part of the CME planning process.

Colorado Foundation of Medical Care will retain a record of attendance on file for six years.

JOINT SPONSOR STATEMENT

This educational activity is jointly provided by Colorado Foundation for Medical Care and the Chicago Dermatological Society.

GOAL / PURPOSE

To educate participants on the new regulations and research surrounding dermatology.

EDUCATIONAL OBJECTIVES

Upon completion of the activity (for the entire series of meetings), participants will be able to:

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

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

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

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CREDIT STATEMENTS

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

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

DISCLAIMER STATEMENTS

The content, views and opinions presented in this educational activity are those of the authors and do not necessarily reflect those of Colorado Foundation for Medical Care and Chicago Ophthalmological Society. The authors have disclosed if there is any discussion of published and/or investigational uses of agents that are not indicated by the FDA in their presentations. Before prescribing any medicine, primary references and full prescribing information should be consulted. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities. The information presented in this activity is not meant to serve as a guideline for patient management.

DISCLOSURE STATEMENTS

Colorado Foundation for Medical Care insures balance, independence, objectivity, and scientific rigor in all our educational activities. In accordance with this policy, CFMC identifies conflicts of interest with its instructors, planners, content managers, and other individuals who are in a position to control the content of an activity.

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

Fee Information - There is no fee for this educational activity.

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CASE # 1A

PRESENTERS
Sogyong Auh, MD, PhD; Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
A 12-year-old Middle Eastern male presented for evaluation and management of alopecia areata. He had previously been managed by an outside dermatologist with intralesional steroid injections. At the first presentation to our office, there were focal patches of hair loss limited to the scalp. Treatment with clobetasol solution for several months resulted in minimal regrowth. The patient did not return for follow-up for two years; in the interim he reported losing all his body and scalp hair, including eyebrows and eyelashes. In the months before he returned for re-evaluation, he noted spontaneous regrowth of his eyebrows and eyelashes.

PAST MEDICAL HISTORY
None

FAMILY HISTORY
Brother with alopecia areata and paternal aunt with thyroid disorder

MEDICATIONS
None

ALLERGIES
No known allergies

PHYSICAL EXAMINATION
Complete absence of hair on scalp, trunk, and bilateral extremities. Eyebrows and eyelashes intact.

LABORATORY DATA
CBC with differential, comprehensive metabolic panel, and thyrotropin within normal limits.

DIAGNOSIS
Alopecia areata, totalis

TREATMENT AND COURSE
Based on reported cases, treatment with hydroxychloroquine was initiated. The patient was started on hydroxychloroquine 200 mg twice daily. The patient reported slight regrowth after 3 months of treatment. After five months, 5% minoxidil solution to the scalp daily was added to the treatment regimen. Significant regrowth was noted after 8 months of treatment with hydroxychloroquine and 3 months of treatment with minoxidil, which became more impressive at 12 months. Initially, the regrown hairs were depigmented, but gradually pigment was restored. Patient also continued use of 5% minoxidil solution to scalp daily.

CASE # 1B

PRESENTERS
Sogyong Auh, MD, PhD; Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
A 14-year-old Middle Eastern male presented for evaluation and management of alopecia areata. He reported patches of hair loss from the scalp ongoing for the past 3 years. Previous treatments included topical and intralesional corticosteroids and 5% minoxidil solution with limited benefit. The patient was very distressed by his hair loss and expressed that this was significantly interfering with his daily life.

PAST MEDICAL HISTORY
None

FAMILY HISTORY
Brother with alopecia totalis and paternal aunt with thyroid disorder

MEDICATIONS
None

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Scattered large patches of hair loss on scalp and bilateral extremities. Eyebrows and eyelashes intact.

LABORATORY DATA
CBC with differential, comprehensive metabolic panel, and thyrotropin within normal limits.

DIAGNOSIS
Alopecia areata, totalis

TREATMENT AND COURSE
Based on reported cases, treatment with hydroxychloroquine was initiated. The patient was started on hydroxychloroquine 200 mg twice daily. After about 3 months, slight regrowth of depigmented hairs was noted. Patient was very pleased with result and was continued on hydroxychloroquine, with recommendation to continue 5% minoxidil solution daily.

DISCUSSION
Alopecia areata (AA) is characterized by non-scarring loss of hair in any hair-bearing area. It is considered a T cell-mediated autoimmune disease, characterized histologically by infiltrating T cells surrounding the hair follicle bulb. In the United States, disease prevalence has been reported to range from 0.1% to 0.2%. The presence of AA is associated with a higher frequency of other autoimmune diseases. The course of AA is often chronic and unpredictable, and the response to treatment may vary.[1,2] A recent case report discussed successful treatment of 2 cases of alopecia totalis with hydroxychloroquine.[11] The first patient was a 40-year-old otherwise healthy female previously treated for AA for 8 years. Past treatments had included topical clobetasol, topical pimecrolimus, and 5% topical minoxidil. However, she evolved to alopecia totalis (AT) and was started on systemic treatment with oral prednisone pulse therapy for 16 months and methotrexate for 11 months. She responded well to the systemic treatments but had recurrence of hair loss when the medications were

weaned. After a 2 month break from treatment, she was started on hydroxychloroquine 200 mg twice a day and after 2 months had significant regrowth. The second patient had a similarly excellent response after 5 months of hydroxychloroquine 200 mg twice a day. Of note, the response was delayed, similar to the observed effect when hydroxychloroquine is used for other autoimmune conditions, such as lupus, where onset of action can be delayed for four to eight weeks. Our patients also seemingly demonstrated delayed onset of action with regrowth at three to six months from the start of therapy. While the possibility of spontaneous regrowth cannot be completely excluded, given the significant response within a few months with minimal side effects, hydroxychloroquine may be a reasonable option for patients with severe alopecia.

Antimalarials have been used widely for the treatment of autoimmune diseases, such as systemic lupus erythematosus. Early studies proposed that chloroquine and hydroxychloroquine functioned by diffusing across cell membranes and raising the pH within cell vesicles, thereby interfering with antigen processing and presentation. Chloroquine and hydroxychloroquine have been shown to inhibit cytokine release in $CD4^+$ T-cell clones *in vitro*.[3,4,5] However, more recent studies suggest an alternative mechanism of immune modulation. Kuznik *et al.*[6] demonstrated that the effect of antimalarials on vesicular pH at concentrations required to block signal transduction was negligible. They also reported that antimalarials did not inhibit endosomal proteolytic processing. Instead, they propose that antimalarials function by affecting endosomal Toll-like receptor (TLR) activation. Chloroquine and quinacrine were able to inhibit TLR9, TLR3, and TLR8 signaling after activation with nucleic acids. A direct interaction between antimalarials and nucleic acid TLR ligands was demonstrated, leading to development of a new mechanistic model. These authors propose that in autoimmune conditions, antimalarials bind to the nucleic acids and mask the TLR binding sites, thus blocking TLR ligand binding and immune activation. Whether similar mechanisms contribute to the efficacy in treatment of AA is yet to be determined.

A recent study investigated the role of cytotoxic T lymphocytes in AA and showed promising preliminary evidence for yet another new treatment approach. Xing *et al.*[8] showed that cytotoxic $CD8^+NKG2D^+$ T cells were both necessary and sufficient for AA in mouse models. Antibody-mediated blockade of interferon-gamma (IFN-γ), interleukin-2 (IL-2) or interleukin-15 receptor β (IL-15Rβ) was effective at preventing AA in mouse models. IL-2 and IL-15 promote cytotoxic activity by IFN- γ-producing $CD8^+$ effector T cells and have been implicated in the induction and maintenance of autoreactive $CD8^+$ T cells.[8] The Janus kinase (JAK) family protein tyrosine kinases are downstream effectors of the IFN- γ receptors. Systemic administration of JAK inhibitors prevented the development of AA, and topical administration was able to reverse established disease in mouse models. Additionally, the study applied the animal model findings by treating three patients with moderate to severe AA with oral ruxolitinib 20mg twice a day, an inhibitor of JAK1 and JAK2.[8] Ruxolitinib is currently FDA-approved for treatment of myelofibrosis. All three patients had almost complete regrowth of hair within 3-5 months of treatment. Additional studies will be needed to further explore the role of JAK signaling and efficacy and safety of JAK inhibitors.

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CASE # 2

PRESENTERS

Adena E. Rosenblatt, MD, PhD; Mara Beveridge, MD; Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS

A nine month old African American boy with a history of a collodion membrane at delivery, now with ichthyosis and multiple medical problems is being followed by dermatology.

PAST MEDICAL HISTORY

Patient was born at 34 and 2/7 week gestation by vaginal delivery following induction for IUGR and oligohydramnios to a 30yo G5P1031 mother. He was born with a collodion membrane that shed as expected. He had transiently elevated transaminases in the NICU. His growth and development upon discharge from the NICU was within normal limits. Since the newborn period, the scalp has continued to have adherent scale and hair is somewhat scant, very short and coarse. Eyebrows are scant but eyelashes are present. Ichthyotic scaling became apparent on his trunk and extremities at 2 months of age. At 2-3 months of age he developed 5 superficial bright red papules and small nodules on his trunk and extremities consistent with infantile hemangiomas.

At 3 months of age the patient was noted to have inguinal lymphadenopathy and subsequently developed cervical and axillary lymphadenopathy in the setting of neutropenia, eosinophilia and elevated transaminases. Lymph node biopsy was consistent with reactive adenopathy and a bone marrow biopsy was within normal limits. Horizontal nystagmus developed and ophthalmologic examination detected decreased vision. By 6 months of age, the infant was manifesting dysmorphic facial features, including bitemporal narrowing, scaphocephaly, frontal bossing, hypertelorism and mildly narrowed and high arched palate, as well as hypotonia, impaired hearing, gastroesophageal reflux and failure to thrive. .

FAMILY HISTORY

No family history of inherited skin conditions or ichthyosis.

MEDICATIONS

Erythromycin ethylsuccinate 20mg PO TID
Famotidine 4.8mg PO TID
Simethicone 20mg PO QID
Multivitamin

ALLERGIES

Mother had an anaphylactic reaction to Ibuprofen so it has been avoided in the patient

PHYSICAL EXAMINATION

Patient was initially evaluated by dermatology at day 2 of life during which time he had a diffuse thin membrane covering his skin without any evidence of restrictive bands and had focal areas of normal skin. He also had ectropion at this time. Patient slowly shed the collodion membrane and subsequently developed persistent diffuse rectangular fish-like scale with mild underlying erythema on the trunk and extremities. He also developed 5 bright red vascular papules and plaques on his extremities and trunk at 2-3 months of age as well as eczematous plaques on his extremities. His exam was also notable for inguinal lymphadenopathy and coarse sparse hairs on scalp and eyebrows. Eyelashes appear normal.

HAIR MOUNT

Trichorrhexis nodosa and trichoschisis were identified on hair mount as well as alternating light and dark bands on polarizing microscopy

LABORATORY DATA

Complete blood count: **(Performed on 2/7/14)** Leukocytes 11.6 K/µL (3.5-17.7), hemoglobin 12.6 g/dL (9.3-13.2), platelets 337 K/µL (150-450)
Differential: Absolute Neutrophils 0.35 K/uL (range Feb 2014-present 0.19-1.35), lymphocytes 75%, monocytes 9%, eosinophils 11%, (range Feb 2014-present 4-14), bands 1%
Glucose 88 mg/dL (60-109), Sodium 140 mEq/L (134-149), Potassium 4.5 mEq/L (3.5-5.0), Chloride 106 mEq/L (95-108), Carbon Dioxide 18 mEq/L (23-30), BUN 8 mg/dL (7-20), Creatinine 0.2 mg/dL (0.5-1.4), Calcium 10.7 mg/dL (8.4-10.2), Total protein 6.1 g/dL (6.0-8.3), Albumin 4.0 g/dL (3.5-5.0), Total bilirubin 0.2 mg/dL (0.1-1.0), Conjugated bilirubin <0.1 mg/dL (0.0-0.3), Unconjugated bilirubin 0.2 mg/dL (0.1-1.0), Serum alkaline phosphatase 694 U/L (100-390), AST 55 U/L (8-37), ALT 75 U/L (8-35)
Bone marrow biopsy 3/26/14 was within normal limits
Lymph node biopsy 3/26/14 showed reactive lymphadenopathy
Skin biopsy 3/26/14 was consistent with an Glut-1 positive infantile hemangioma
Magnetic Resonance Imaging of the brain 7/18/14 showed apparent delayed myelination for adjusted age but intact midline structures. Skull is dolichocephalic

DIAGNOSIS

Trichothiodystrophy

TREATMENT AND COURSE

Patient has been enrolled in the genetic study of diseases of keratinization at Yale University and we are awaiting genetic testing results. His ichthyosis is currently being managed with emollients. His eczematous dermatitis is well controlled with topical steroids and his hemangiomas are stable becoming slightly softer and lighter in color. He is being treated by physical, occupational and speech therapy for his developmental delay. Neurology is is following the patient for his hypotonicity, ophthalmology for his nystagmus, and hematology for his neutropenia and eosinophilia that continues to wax and wane. Patient also recently had a gastrostomy-tube placed to better address his nutritional needs and is being followed regularly by gastroenterology.

DISCUSSION

Trichothiodystrophy (TTD) is a rare autosomal recessive disease. It is due to a mutation in a variety of DNA repair genes including XPB, XPD, TTDA, and TTDN1. These mutations lead to a reduced level of the repair/transcription factor TFIIH resulting in depressed RNA synthesis. Interestingly, XPD and XPB are also mutated in xeroderma pigmentosum (XP). However, unlike XP, an increased risk of skin cancers is not associated with TTD. There is an equal gender distribution observed in TTD. This syndrome initially was referred to by the acronym BIDS (brittle hair, intellectual impairment, decreased fertility, and short stature) in 1976. This acronym was then changed to IBIDS when ichthyosis was added and subsequently PIBIDS when photosensitivity was included. The name trichothiodystrophy was first proposed in 1979 by Vera Price and refers to the low sulfur content in the hair of patients with TTD.

Hair abnormalities are the most common finding in TTD and the defining feature. The characteristic microscopic feature of “tiger tail banding” is the alternating light and dark banding pattern seen under polarizing microscopy. A variety of additional hair abnormalities can be present in this condition including trichorrhexis nodosa and trichoschisis. Regardless of the type of hair abnormality, all of the abnormal hairs have low sulfur content. There is also no correlation between disease severity and

percent of abnormal hairs.

The majority of TTD patients have skin findings. The most common finding is ichthyosis (65%) followed by photosensitivity (42%). Patients that have photosensitivity develop sunburns with minimal UV exposure. Collodion membrane is observed in about a quarter of patients with TTD. Additional skin findings reported in TTD include xerosis, eczema, freckles and rarely hemangiomas and cheilitis. Many patients with TTD also have nail abnormalities, most commonly onychodystrophy, but a subset may demonstrate hypoplasia and koilonychia.

Developmental delay has been reported in 86% of patients, including impaired motor control and psychomotor retardation. Other neurologic findings include microcephaly, abnormal gait, increased deep tendon reflexes and hearing loss. These neurologic findings may be associated with neuroimaging abnormalities including dysmyelination, cerebellar atrophy, and dilated ventricles.

About 80% of patients with TTD have short stature and/or poor weight gain. About half of patients have ocular abnormalities the most common being cataracts followed by nystagmus and strabismus. The majority of these patients require corrective lenses. Less commonly there may be joint or skeletal abnormalities including osteosclerosis, delayed bone age, contractures, joint dislocation, and osteopenia. Hematologic abnormalities are also uncommon but include anemia and neutropenia. Cardiac and hepatic abnormalities are rare.

There is a 20-fold higher mortality rate in patients with TTD at 9 years of age compared to the general population. The leading cause of death is due to infection. An overall increased risk of infection in these patients has been noted, but the mechanism is unclear. Since TTD can affect many different organ systems it is important to take a multidisciplinary approach to caring for these patients.

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CASE # 3

PRESENTERS

Olga Radkevich-Brown, MD, PhD; Arlene Ruiz de Luzuriaga, MD, MPH; Vesna Petronic-Rosic, MD, MSc

HISTORY OF PRESENT ILLNESS

41 year-old African American female presented to the dermatology clinic with a 2-month history of "skin bumps." They enlarged and coalesced into distinct plaques, one on each thigh. The affected areas were asymptomatic, and there was no ulceration, drainage, or bleeding. Review of systems was unremarkable, and the patient was otherwise well.

PAST MEDICAL HISTORY

Hypertension, hyperlipidemia, diabetes mellitus type 2

FAMILY HISTORY

Positive for atopy in daughter and mother.

MEDICATIONS

Amlodipine/valsartan/hydrochlorothiazide
Atorvastatin
Metoprolol XL
Metformin.

ALLERGIES

Penicillin

PHYSICAL EXAMINATION

Left anterior thigh with a cluster of dark brown violaceous papules and nodules coalescing into a firm round plaque of 10 centimeters in diameter. Right posterolateral thigh with similar plaque of 4 centimeters in diameter.

DERMATOPATHOLOGY

Initial biopsy (left thigh): Dense collections of epithelioid histiocytes are present throughout the dermis. Focally, there is caseous necrosis with karyorrhectic debris, surrounded by well defined, palisading granulomas. A dense perivascular lymphocytic infiltrate is noted in the surrounding tissue. The colloidal iron stain demonstrates a normal amount of dermal mucin. The PAS, GMS, Gram and Fite stains are negative. Polarized light examination is negative for birefringent foreign material.

Subsequent biopsy, 6 months after the initial presentation (left thigh): Throughout the dermis and extending into the subcutaneous fat are discrete collections of histiocytes forming granulomas, adjacent to lymphoid clusters with numerous plasma cells. There is no significant atypia of the lymphoid cells. The PAS, GMS, gram and Fite stains are negative. Immunohistochemical evaluation for Treponema pallidum is negative. Polarized light examination is negative for birefringent foreign material. Anti-CD3 immunolabels ill-defined clusters of T lymphocytes. Anti-CD20 immunolabels discrete collections of B cells, which are significantly more in numbers that T cells. Anti-CD68 antibody immunolabels numerous histiocytes forming discrete granulomas throughout the dermis and subcutaneous fat. Anti-S100 and anti-CD1a antibody immunolabels scattered Langerhans cells in the epidermis and dermis. Anti-factor XIIIa antibody focally immunolabels scattered dermal dendrocytes. Kappa to lambda light chain ratio is 2-3:1. Anti-tryptase antibody immunolabels scattered mast cells. There is strong staining for IgG throughout the specimen, and IgG4 accounts for less than 10% of total

IgG.

Molecular diagnostic studies: polyclonal B cell and T cell proliferation, although a small T cell clone was detected.

Dermatopathology consultation microscopic description: Histologic sections demonstrate a diffuse histiocytic infiltrate with nodular lymphoplasmacytic aggregates. There is no evidence of light chain restriction in a mix of B- and T-cells within aggregates. The histiocytes demonstrate some evidence of emperipolesis. Many of the histiocytes contain vacuoles with amorphous material.

LABORATORY DATA

Complete blood count: Leukocytes 8.2 K/µL (3.5-11), hemoglobin 10.7 g/dL (9.8-17.6), MCV 76.9 (81-99)
C-reactive protein: 24 mg/L (NL<5)
Tissue culture: normal skin flora
Tissue AFB smear and culture: negative
Tissue fungal smear and culture: negative
Blastomyces Ab by immunodiffusion: negative
Histoplasma urine antigen: negative
Tissue PCR for bacterial, fungal, tuberculous and non-tuberculous mycobacterial DNA: negative
Quantiferon-TB Gold: negative
HIV: non-reactive
RPR: non-reactive
SPEP: gamma globulin 1.60 g/dL (1.0-1.5), no monoclonal spike
Immunoglobulin G: 1768 mg/dL (800-1700); IgA and IgM within normal limits
Tryptase: 2.9 ng/ml (<11.5)

DIAGNOSIS

S100-negative cutaneous Rosai-Dorfman disease

TREATMENT AND COURSE

As the initial biopsy showed granulomatous dermatitis with caseous necrosis concerning for an infectious process, despite negative stains and cultures for microorganisms, the patient was empirically started on doxycycline 100 mg twice daily.

At the 6-month follow-up, the lesions were stable in size but had become tender to touch. Doxycycline was discontinued due to lack of efficacy, and a second biopsy was obtained. It demonstrated plasma cell-rich granulomatous dermatitis, with a negative infectious workup. The granulomatous nature of the condition still raised suspicion for possible mycobacterial infection, and an infectious disease consultation was obtained. Additional limited malignancy and endemic fungal workup was performed, with negative results. A dermatopathology consultation was obtained, which yielded a presumptive diagnosis of non-X histiocytosis similar to cutaneous Rosai-Dorfman.

At 14 months, the left anterior thigh plaque was increased in size and more papules and nodules had appeared within it. A test area was injected with 0.5 ml of intralesional triamcinolone acetonide 20 mg/ml.

DISCUSSION

Non-Langerhans cell histiocytoses, also known as non-X histiocytoses or histiocytoses of mononuclear phagocytes other than Langerhans cells, are disorders with macrophage/monocyte proliferation. Histiocytes are considered tissue resident macrophages derived from blood monocytes.

Non-X histiocytoses include several rare entities that are distinguished based on expression of surface markers, cutaneous and/or systemic involvement, and clinical course. All non-X histiocytoses have a CD68 positive and CD207 (Langerin) negative phenotype, with variable expression of S100 and factor XIIIa. Positive CD1a immunolabeling is observed in indeterminate cell non-X histiocytosis.

Rosai-Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy, is a benign, proliferative disorder of histiocytes of unknown etiology. It was originally described in children and young adults with male predominance. It is characterized by massive lymphadenopathy. Skin lesions are present in 10% of patients, usually multiple, on the face, and are commonly associated with fever, anemia, polyclonal hypergammaglobulinemia, and an elevated sedimentation rate. A purely cutaneous variant has been increasingly recognized. It is predominantly seen in adult women. Skin lesions can be solitary or multiple, with no site predilection. These patients lack lymphadenopathy or systemic findings. Both systemic and cutaneous variants have the same histopathologic characteristics – presence of large pale histiocytes, which are CD68 and S100 positive, and CD1a and Factor XIIIa-negative, mixed plasma cell-rich inflammatory infiltrate, and emperipolesis.

Immunohistochemistry in our patient revealed a CD68 positive, S100 negative, CD1a negative and factor XIIIa negative phenotype. Her gender, adult age of onset with focal, exclusively cutaneous involvement, morphology and location of the lesions, as well as findings of large pale histiocytes, plasma-cell rich infiltrate, and emperipolesis, favor the diagnosis of cutaneous Rosai-Dorfman disease. There are no published reports of S100-negative Rosai-Dorfman disease; however, atypical expression of S100 was reported in otherwise S100-negative non-X histiocytoses.

Treatment: Cutaneous Rosai-Dorfman follows a benign, although sometimes persistent course and thus treatment is usually not medically necessary. Previously described treatment options include surgical excision for small solitary lesions, cryotherapy, radiation therapy, isotretinoin, thalidomide, topical, oral, and intralesional corticosteroids.

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CASE #4A

PRESENTERS
Eduardo K. Moioli, MD, PhD; Christopher R. Shea, MD; Keyoumars Soltani, MD; Diana Bolotin, MD, PhD

HISTORY OF PRESENT ILLNESS
34 year old female presented with an "itchy scar" located on the right cheek. Patient reported that a benign cyst had been excised from the right cheek about 10 years prior. Scar healed well initially but more recently developed intermittent "deep itching". She denied numbness or pain. There was a firm area that had enlarged slowly over time beneath the site of the prior excision. The patient was otherwise feeling well and denied fevers, chills, lymphadenopathy, or weight loss.

PAST MEDICAL HISTORY
None

MEDICATIONS
None

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
Right cheek with a 2 cm, firm and indurated non-tender smooth nodule tethered to the superficial skin. Nodule was deep to a small hypopigmented ovoid scar (site of prior excision).

DERMATOPATHOLOGY
Poorly-circumscribed, deeply infiltrating tumor composed of superficial keratocysts and solid strands of cells without significant atypia, many of which had ductular lumina or keratinous cystic formations in a dense fibrous stroma. No frank perineural invasion was identified, however tumor cells were observed in proximity to a nerve fascicle. A single mitotic figure was identified. Anti-CK19 antibody immunohistochemical stain labeled tumor cells strongly and diffusely, whereas anti-BerEP4 antibody immunostain was negative.

IMAGING
MRI: Irregular enhancing lesion in the skin and subcutaneous tissues of the anterior right cheek adjacent to the nasolabial fold measuring 6mm AP x 13mm RL. There was no evidence of involvement of the underlying bone or perineural spread of tumor. No evidence of significant regional lymphadenopathy. Orbits and intracranial structures were unremarkable.

DIAGNOSIS
Microcystic adnexal carcinoma

TREATMENT AND COURSE
Upon histopathologic diagnosis of microcystic adnexal carcinoma, treatment options were discussed including complete excision with Mohs micrographic surgery (MMS) and radiation therapy as single therapy or as adjuvant therapy. MMS was recommended as initial treatment. The tumor was subsequently completely excised in 4 stages with clear margins obtained on frozen sections and confirmatory permanent sections of the last stage. Given clear surgical margins and risks of adjuvant radiation therapy likely outweighing benefits, further treatment was deferred.

CASE # 4B

PRESENTERS
Eduardo K. Moioli, MD, PhD; Christopher R. Shea, MD; Keyoumars Soltani, MD; Diana Bolotin, MD, PhD

HISTORY OF PRESENT ILLNESS
81 year old female presented for evaluation of a red, thickened, rash-like area on the central forehead that started approximately 8 months prior. The affected area had enlarged over time and became pruritic. Prior treatments included over-the-counter hydrocortisone, which alleviated the pruritus but not the redness and enlargement of the thickened area continued. She had three prior biopsies by an outside dermatologist with diagnoses of: (1) focal epithelial cell proliferation and surrounding keratin granulomas/chronic inflammation, (2) multiple keratin granulomas and (3) squamous cell carcinoma. The patient had a 10-15 pound weight loss over the past year.

PAST MEDICAL HISTORY
Multiple basal cell carcinomas and squamous cell carcinomas treated surgically, hypertension, hyperlipidemia, diabetes mellitus type 2, overactive bladder

MEDICATIONS
Amlodipine 5mg PO daily, aspirin 81mg PO daily, citalopram 10mg PO daily, clonidine 0.2mg PO twice daily, clopidogrel 75mg PO daily, lisinopril 40mg PO daily, metformin 500 mg PO twice daily, metoprolol 100mg PO daily, simvastatin 10mg PO daily, tolterodine 2mg PO twice daily

ALLERGIES
Alprazolam, fentanyl, midazolam

PHYSICAL EXAMINATION
Central forehead and glabella with 6-centimeter irregularly shaped pink-erythematous thin plaque with mildly elevated papular borders and scattered < 3 mm papules within it.

DERMATOPATHOLOGY
Four punch biopsies of the forehead plaque were performed and showed poorly-circumscribed, infiltrating tumor composed of superficially located, small to medium-sized keratocysts, and solid strands of cells, many of which demonstrate ductular formations. Tumor cells exhibited considerable cytologic atypia and a high number of mitotic figures. Frank perineural invasion was not identified. There were focal multinucleated giant cells palisading around keratin fragments. Anti-MNF116 antibody strongly immunolabeled the epidermis, eccrine gland epithelium and the atypical neoplastic cells in the dermis.

IMAGING
MRI: 6 cm wide area of skin thickening in the middle and left frontal scalp with ill-defined areas extending into the subcutaneous tissues. The underlying calvarium appeared intact.
CT chest and upper abdomen: No evidence of metastases.

DIAGNOSIS
Microcystic adnexal carcinoma

TREATMENT AND COURSE
Treatment options including Mohs micrographic surgery with likely operating room reconstruction given the clinical size and radiation were discussed. Due to the large clinical size with likely extensive

subclinical extension given the diagnosis, location on the central face, and patient comorbidities and age, the patient and her family elected a non-surgical approach to treatment. She was treated with radiation therapy with 6 MeV electrons to a cumulative dose of 7000 cGy to gross disease area using 2 Gy daily fractions, Mondays through Fridays for 6.5 weeks. Limiting factors included proximity to the orbit, which reduced the desired radiation treatment margin of 2-3 centimeters around clinically visible extent of disease. The patient tolerated therapy well overall, with grade 2 skin reaction of brisk erythema and dry desquamation.

DISCUSSION

Microcystic adnexal carcinoma (MAC) is a low-grade form of adnexal carcinoma of pilar and sweat gland differentiation typically arising in young or middle-aged adults. It is slightly more prevalent in women and most are found in the head and neck[1]. It has been postulated that UV light and other radiation may have an etiologic role as these tumors have a predilection for the left side of the face (related to UV light exposure while driving) and have been described in multiple case reports of patients previously treated with radiation therapy. Tumors typically enlarge slowly over many years and are often initially misdiagnosed. Most frequently, these tumors are initially diagnosed as squamous cell carcinomas or benign tumors such as syringomas as a result of a superficial biopsy [1]. The present two cases demonstrate this pitfall with one case being previously diagnosed as a benign lesion by an outside practitioner many years prior and another with repeated inconclusive biopsies.

Clinically, MAC presents as a smooth-surfaced and flesh-colored to yellowish nodule, papule, plaque, or cystic lesion. It may be asymptomatic, or as seen in the present two cases, pruritic. Other reported symptoms include numbness, paresthesia, and burning, presumably as a consequence of neural invasion. The tumor tends to gradually grow over time but may have a period of more rapid growth [1].

Histologically, MAC demonstrates ductal components along with follicular features and sporadic sebaceous differentiation. It demonstrates a stratified appearance with larger keratin horn cysts and epithelial cords in the superficial dermis surrounded by a desmoplastic stroma, and more ductal structures in the deeper dermis. Cytologic atypia is uncommon. A distinguishing feature is the extensive infiltration of the reticular dermis and perineural invasion. The tumor invasion typically extends well beyond the clinically visible margin and also deeply to the subcutaneous fat, significantly impacting treatment considerations. Previous reports of tumor margins have varied widely from a few millimeters to 3-5cm[1].

Treatment options include observation given its indolent course, standard excision, Mohs Micrographic Surgery (MMS), and radiation. MMS has been the preferred treatment modality with the highest rate of complete clearance and overall most advantageous outcomes including lower rates of recurrence and need for re-excision. Prior case series have reported that 30% of patients treated with standard excision required additional procedures due to positive margins on the excision specimen. Other studies have reported rates of recurrence after standard excision ranging from 40 to 60%. Rates of recurrence are much lower in patients treated with MMS, ranging from 0 to 22% as compiled from multiple reports in the literature[2]. Clear margins are obtained on an average of 3 stages (range from 1-7)[3]. Recurrence occurs most commonly within the first 2–3 years after initial treatment but recurrence after as long as 30 years has been reported[4].

Treatment options are more limited in cases of large-sized tumors where surgical excision may lead to significant morbidity as seen in the second case presented in this series. Prior reports have advocated for clinical monitoring only[5], but these recommendations may have been based on lack of expertise with, and lack of availability of, newer radiation therapy techniques. Although rates of metastasis and death from MAC are very low, it is often difficult to predict patients' longevity and patients most often prefer treatment over observation. In cases with potential significant disfigurement from surgery,

monotherapy with radiation has been reported as an option. The recommended dose is of 66 to 70 Gy in standard fractionation with a treatment area that includes the clinically visible lesion and a margin of approximately 3 cm to account for the subclinical lesion[6]. Importantly, in most of the reported cases, recurrence was a common feature of monotherapy with radiation. Alternatively, radiation may be utilized as adjuvant therapy to MMS in cases where clear margins cannot be obtained or those with extensive perineural invasion[7]. In one case of a large MAC located on the face treated with surgery and adjuvant radiation, there was no recurrence noted after a period of 3 years.

Unfortunately, there is no available data on the unique survival rates associated with each treatment modality. In a review of survival rates for patients with cutaneous adnexal carcinomas with eccrine differentiation including MAC, hidradenocarcinoma, spiradenocarcinoma, porocarcinoma, and eccrine adenocarcinoma, the overall reported 5-year survival for patients with MAC was 90% not stratified by treatment modality. Among all adnexal carcinomas evaluated, treatment with surgical excision or with excision plus radiation had comparable survival rates (not stratified between MMS and standard excision)[8].

In conclusion, we illustrate two cases of MAC with significantly different clinical presentations and demographics leading to different treatment decisions. Mohs surgery should still be considered as the first line treatment; however, individual case circumstances may limit the use of surgical treatments leading to consideration of alternatives such as monotherapy with radiation. While radiation may be an effective alternative, we emphasize the need for continued surveillance given the higher rates of recurrence. Lastly, patients undergoing MMS for MAC that demonstrate high risk features such as extensive perineural invasion, significant depth of involvement, and relatively high mitotic rate, should be considered for post-operative adjuvant radiation therapy.

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CASE # 5

PRESENTERS

Min Deng, MD; Vesna Petronic-Rosic, MD, MS; Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS

A 23-year old Caucasian female with a history of oculocutaneous albinism and nodular melanoma of the right posterior calf, diagnosed in Dec. 2013, presented to us for skin cancer screening. During her exam she expressed interest in removing a fleshy outgrowth on the right proximal medial thigh which had been present for approximately 4 to 5 years but had gotten slightly larger in the previous few months and was getting irritated due to its location and constant rubbing. Due to her extreme photosensitivity, our patient reported that she generally avoids the sun and uses SPF 45 or higher on a regular basis. However, she did have a blistering sunburn limited to the face as a child and approximately one mild sunburn annually, typically limited to her posterior neck and upper shoulders..

PAST MEDICAL HISTORY

Oculocutaneous albinism
Nodular melanoma (T3a/N0/M0 - 2.08mm, 4 mitoses/mm^2, Clark IV, with 0/3 SLN) s/p wide local excision
Multiple biopsy-proven dysplastic nevi
Hashimoto's thyroiditis

FAMILY HISTORY

Oculocutaneous albinism (sister)
Non-melanoma skin cancer (paternal grandfather)
Non-Hodgkin's lymphoma (father)

MEDICATIONS

Escitalopram qd
Lorazepam PRN

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

On exam, an 8 mm flesh-colored smooth soft pedunculated papule was noted on the right medial proximal thigh.

DERMATOPATHOLOGY

Biopsy:

A shave biopsy demonstrated a compound melanocytic nevus, which appeared symmetric with progressive maturation of melanocytes. Nests of melanocytes without significant cytologic atypia or mitotic figures were present at both the dermal-epidermal junction and in the dermis. Scattered giant multinucleated melanocytes were appreciated at higher magnification. Increased numbers of single melanocytes were noted along the dermal-epidermal junction. Anti-MelA/Ki67antibodies co-labeled fewer than 5% of the melanocytes, predominantly at the dermal-epidermal junction. HMB-45 antibody demonstrated gradual loss of staining within the dermis. While a histologic diagnosis of a nevus was favored, the atypical features of increased number of single cells along the dermal-epidermal junction and Ki-67 positivity prompted a recommendation for re-excision.

Excision:
Histopathologic examination of the excision specimen revealed a poorly circumscribed asymmetrical proliferation of melanocytes arranged in irregular nests as well as single cells at the basal layer of the epidermis. The melanocytes had severely atypical cytologic features and demonstrated suprabasal spread. Several dermal mitotic figures were identified. Anti-MelA/Ki67 antibodies co-labeled numerous melanocytes in the epidermis and dermis.

Based on these histologic features, our patient was diagnosed with invasive melanoma, superficial spreading type (Breslow depth 2.3 mm, $\geq$ 2 mitotic figures/mm^2).

Sentinel lymph node biopsy:
No evidence of tumor in 1 sentinel lymph node
No evidence of tumor in 1 non-sentinel lymph node

IMAGING AND LABORATORY DATA
CT Chest, abdomen, pelvis with contrast – within normal limits
Next generation sequencing – BRAF V600E mutation present

DIAGNOSIS
Second primary invasive melanoma in a patient with oculocutaneous albinism

TREATMENT AND COURSE
Our patient's 2nd primary melanoma was staged as T3aN0M0 (Stage IIA) and she was treated with wide local excision. After further consultation with our medical oncologist, the decision was made to pursue clinical monitoring with repeat skin exams every 3 months.

Approximately 5 months later, our patient returned for evaluation of 2 enlarging lesions. The first, a lightly pigmented oval-shaped lesion on the left clavicle, was biopsied and diagnosed as a predominantly intradermal nevus. The second, a pink plaque with central hairs that she's had since birth on the lower back, was biopsied and diagnosed as a compound melanocytic nevus with severe cytologic atypia.

We will continue to monitor her clinically every 3 months.

DISCUSSION
Oculocutaneous albinism is a rare genetic disorder of pigmentation, which is associated with increased photosensitivity and increased risk for skin cancer. Despite the overall increased risk for skin cancer, however, the incidence of melanoma remains low for patients with oculocutaneous albinism.[1,2] Between 1888 and 2001 only 26 cases of melanoma had been reported in patients with oculocutaneous albinism in the English literature.[2] The youngest reported case was in an 8-year-old boy who presented for evaluation of a new growth on the ear.[3] In a 10-year histological retrospective study of skin cancers from patients with oculocutaneous albinism at a Northern Tanzania referral hospital, squamous cell carcinomas were the most common type of skin cancer (72/134, 53.7%), followed by basal cell carcinomas (61/134, 45.5%), with only 1 case of melanoma, acral lentiginous type (0.75%).[4]

We present this patient for clinical interest and to highlight the difficulty in clinically identifying dysplastic nevi and melanomas in patients with physical findings consistent with oculocutaneous albinism type 1. Even our patient's initial biopsy was misleading as the architecture and cytology were considered overall benign outside of the atypical finding of increased single melanocytes in certain sections. The patient's initial primary melanoma was also a flesh-colored pedunculated papule which was biopsied due to her complaint of it having recently become more raised. Her history of two

independent primary melanomas and numerous biopsy-proven dysplastic nevi suggest an underlying p16 mutation. We are currently pursuing further genetic testing. In the meantime our patient remains vigilant with self-monitoring and has been vital in reporting any new or changing growths that would prompt a biopsy.

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CASE # 6

PRESENTERS

Alex Means, MD; Vesna Petronic-Rosic, MD, MSc; Sarah L. Stein, MD

UNKNOWN

CASE # 7

PRESENTERS
Duri Yun, MD; Arlene Ruiz de Luzuriaga, MD, MPH; Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
A 2yo girl, with no significant past medical history, presented with a 3-week history of a persistently itchy rash associated with intermittent fevers to 102F, and joint pain and swelling. The rash was described as red and bumpy, initially involving torso and extremities. Her cutaneous symptoms did not remit with defervescence and did not improve with the use of emollients, oral antihistamines or hydrocortisone 1% cream.

PAST MEDICAL HISTORY
None

FAMILY HISTORY
Rheumatoid arthritis in maternal cousins

MEDICATIONS
Benadryl
Hydrocortisone 1% cream

ALLERGIES
Amoxicillin

PHYSICAL EXAMINATION
The patient was febrile with a temperature of 38.5C, with the rest of her vital signs within normal limits. The patient appeared uncomfortable at rest. Physical examination revealed bilateral swelling and tenderness of the knees. Movement of her joints elicited pain. Her left hand digits and wrist showed edema with pain on wrist flexion and extension. Skin examination revealed erythematous and hyperpigmented linear plaques in a flagellate pattern with underlying xerosis involving the dorsal feet, anterior knees, antecubital arms, flanks and lower back.

DERMATOPATHOLOGY
A skin biopsy was obtained from an involved area on the leg. Histopathology revealed dyskeratotic keratinocytes arranged singly and in clusters in the stratum corneum and upper spinous layer of the epidermis. There was mild spongiosis of the epidermis and a sparse superficial dermal perivascular, periadnexal and interstitial mixed cell infiltrate composed of lymphocytes, histiocytes and neutrophils. Ectatic vessels were noted in the superficial papillary dermis. Fungal and bacterial stains were negative. PAS stains were negative for basement membrane thickening.

LABORATORY DATA
Complete blood count: Leukocytes 38.2 K/µL (3.5-17.7), hemoglobin 8.6 g/dL (9.8-17.6), platelets 718 K/µL (150-450)
Differential: Neutrophils 84%, lymphocytes 5%, monocytes 2%, eosinophils 2%, bands 5%
Complete metabolic panel: Glucose 100 mg/dL (60-109), **sodium 131 mEq/L (134-149),** potassium 4.4 mEq/L (3.5-5.0), **chloride 94 mEq/L (95-108), carbon dioxide 22 mEq/L (23-30),** BUN 12 mg/dL (7-20), creatinine 0.3 mg/dL (0.5-1.4), total bilirubin 0.1 mg/dL (0.1-1.0), **total protein 8.6 g/dL (6.0-8.3), albumin 3.4 g/dL (3.5-5.0), AST 55 U/L (8-37)**, ALT 31 U/L (8-35), **alkaline phosphatase 179 U/L (30-120)**
Ferritin: 2558 ng/mL (10-220)

Erythrocyte sedimentation rate: 117 mm/h (0-20)
C-reactive protein: 68 mg/L (<5)
D-dimer assay: 2.46 ug/mL (<0.4)
Echocardiogram: mild pericardial effusion, with prominence and ectasias of left anterior descending coronary artery
Bone marrow biopsy: normal
Cerebrospinal fluid: normal
Infectious disease work up: negative

DIAGNOSIS
Flagellate erythema in the setting of acute onset systemic juvenile idiopathic arthritis

TREATMENT AND COURSE
The patient was initially treated at an outside hospital with a preliminary diagnosis of Kawasaki's disease due to fevers and echocardiogram abnormalities. The patient received 2 doses of intravenous immunoglobulins without improvement of her fevers or rash. Due to persistent fevers, rash and synovitis, the patient was diagnosed with juvenile idiopathic arthritis complicated by low grade macrophage activating syndrome and transferred to our facility for further care. The patient was started on pulsed steroids with solumedrol 2mg/kg IV daily for a 3 day course with correlating decrease in serologic markers. Upon discharge, the patient was continued on oral prednisolone 2mg/kg/day as well as monthly injections of canakinumab, a human monoclonal antibody to interleukin-beta. Aspirin was started due to echocardiogram findings concerning for prominence and ectasias of the left anterior descending coronary artery. Cutaneous symptoms were treated with topical triamcinolone 0.1% ointment and anti-histamines for symptomatic relief. One month into treatment, systemic and cutaneous symptoms had resolved and laboratory results had returned to baseline. After two months of treatment, the aspirin was discontinued when a repeat echocardiogram showed resolution of cardiac abnormalities. The patient continues to be treated with once monthly canakinumab and has nearly completed a prednisolone taper without recurrent symptoms since presentation.

DISCUSSION
Systemic JIA is a diagnosis of exclusion and is defined as arthritis with or preceded by daily fevers of at least 2 weeks duration with at least one of the following systemic signs of inflammation: non-fixed erythematous eruption, generalized lymphadenopathy, serositis or hepatosplenomegaly. [1] Coronary artery dilatation has also been well described in pediatric cases of systemic onset JIA. [2] The classic exanthem associated with systemic JIA is evanescent salmon-pink papules that arise with fevers and resolve within hours of defervescence. This eruption is not typically pruritic.

A review of the literature reveals that the distinctive feature of flagellate erythema has been described in adult-onset Still's disease. Flagellate erythema is typically described as linear pigmented slightly scaly streaks and classically associated with bleomycin exposure, dermatomyositis and shiitake mushroom ingestion. The patients described in the literature presenting with flagellate erythema in the setting of adult-onset Still's disease were noted to demonstrate similar erythematous, mildly scaly plaques in a linear configuration. The histologic findings were notable for the unusual finding of dyskeratotic keratinocytes in the upper layer of the epidermis and extending into the stratum corneum. This morphology has not been previously reported in children presenting with acute onset systemic JIA. [3-7] The pathophysiology of flagellate erythema is poorly understood, but is thought to be a Koebner phenomenon associated with minor trauma or physical injury or sun exposure. [8] The linear pattern suggests that scratching may be the inciting trauma that then becomes koebnerized. This case

highlights an atypical cutaneous presentation of acute onset systemic JIA and another potential differential diagnosis for flagellate erythema in the pediatric population.

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CASE # 8

PRESENTERS
Mara G. Beveridge, MD; Vesna Petronic-Rosic, MD, MSc

HISTORY OF PRESENT ILLNESS
The patient is a 58 year-old Caucasian female with a history of chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) maintained on ibrutinib therapy that presents with a rash of 6 months duration. The rash is described as small raised bumps that are occasionally itchy located on her arms, legs, trunk, and face. She notes hair loss at the sites of the rash. She has been on ibrutinib therapy for 1 year.

PAST MEDICAL HISTORY
CLL/SLL, hypertension, hyperlipidemia, depression, anxiety

FAMILY HISTORY
Non-contributory

MEDICATIONS
Ibrutinib, atenolol, simvastatin, montelukast, desloratadine, venlafaxine, lorazepam, naproxen, acetaminophen, acetaminophen/diphenhydramine

ALLERGIES
Sulfa

PHYSICAL EXAMINATION
Many pinpoint folliculocentric papules with thin central spine located on arms, legs, and trunk

DERMATOPATHOLOGY
Sections are of skin with orthokeratosis. There are two dilated follicular infundibula with keratotic plugging. There is lack of hair shaft formation.

LABORATORY DATA
Complete blood count: Leukocytes 4.1 K/μL (3.5-11), hemoglobin 12.6 g/dL (11.5-15.5), platelets 406 K/μL (150-450)
Differential: Neutrophils 51%, lymphocytes 35%, monocytes 8%, eosinophils 5%, myelocyte 1%
Basic metabolic panel: Glucose 182 mg/dL (60-109), sodium 140 mEq/L (134-149), potassium 4.3 mEq/L (3.5-5.0), chloride 102 mEq/L (95-108), bicarbonate 28 mEq/L (23-30), anion gap 10 mmol/L (6-15), blood urea nitrogen 13 mg/dL (7-20), creatinine 0.6 mg/dL (0.5-1.4), glomerular filtration rate estimate (calculated) 103 mL/min/BSA (>59), calcium 9.4 mg/dL (8.4-10.2)
Hepatic function panel: Total protein 6.3 g/dL (6.0-8.3), albumin 3.9 g/dL (3.5-5.0), total bilirubin 0.3 mg/dL (0.1-1.0), alkaline phosphatase 104 U/L (30-120), aspartate aminotransferase (AST) 20 U/L (8-37), alanine aminotransferase (ALT) 26 U/L (8-35)
Lactic dehydrogenase: 350 U/L (116-245)
Uric acid: 4.6 mg/dL (2.0-7.5)

DIAGNOSIS
Trichodysplasia spinulosa

TREATMENT AND COURSE

Since the patient was only mildly symptomatic, we initially opted for conservative therapy with lactic acid 10% topical cream to be used twice daily to the affected areas on arms, legs, and trunk and acyclovir 5% ointment to be used twice daily to the affected areas on face. She could not tolerate the acyclovir ointment on the face, due to a burning sensation.

DISCUSSION

Trichodysplasia spinulosa is a rare skin condition in immunosuppressed patients that was first reported by Haycox and colleagues in 1999. It is characterized by hyperkeratotic white-yellow follicular spicules that show viral changes with coarse trichohyaline granules in addition to absence of the hair shaft and disordered follicular keratinization on histopathology. A viral association with polyomavirus has been confirmed.

In the last 15 years alone the number of known polyomaviruses have increased from 10 species to 30 species. They are thought to be ubiquitous and generally do not cause disease for the host unless the immune system is compromised. There are four strains of polyomavirus known to cause disease in humans; they are BK polyomavirus, JC polyomavirus, Merkel cell polyomavirus, and trichostasis spinulosa-associated polyomavirus. The seroprevalence of trichodysplasia-associated polyomavirus in the general population, according to one study, is 41% in children aged 0-9 years old and 75% in adults aged 30 years and older; this is comparable to the seroprevalence of other polyomavirus species.

Traditionally, trichodysplasia spinulosa has been associated with immunosuppression related to solid organ transplantation, but it has recently been reported in patients with acute and chronic lymphocytic leukemia as well. Chronic lymphocytic leukemia (CLL) is caused by B cell dysfunction and is associated with immunosuppression, the cause of which is thought to be multifactorial including hypogammaglobulinemia, low complement levels, altered leukemia-cell expression of major histocompatibility complex class II antigens, impaired granulocytic function, functional defects in bystander T cells, altered expression of T-cell receptor variable region genes, and leukemic B cells producing immunosuppressive factors.

Treatments for CLL can also be immunosuppressive and there are several case reports in the literature that describe trichodysplasia spinulosa during chemotherapy with cytotoxic agents, with onset after initiation and complete resolution after completion. Ibrutinib, the chemotherapeutic agent used by our patient, is in a newer class of targeted chemotherapies. It works by selectively and irreversibly inhibiting Bruton's tyrosine kinase (Btk), one of the tyrosine kinases that is thought to be constituitively active and over-expressed in CLL. By inhibiting Btk, downstream activation of the B cell receptor pathway is repressed and proliferation and survival of malignant B cells is prevented. The most common side effects of ibrutinib therapy are diarrhea, bruising, upper respiratory tract infection, hyperuricemia, and fatigue (all with an incidence of greater than 30%). Skin rash has been described in 27% of patients, but the type of rash is not specified and trichodysplasia spinulosa specifically has not been reported to our knowledge.

While it is possible that the skin findings of trichodysplasia spinulosa in our patient may be associated with her CLL, the onset of symptoms after initiation of ibrutinib therapy suggests that it may be more specifically related to this agent which has an immunomodulating effect. This hypothesis would be further supported if her skin lesions resolved completely after discontinuing ibrutinib; though, there is no current plan to do so.

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CASE # 9

PRESENTERS
Haider K. Bangash ,MD; Vesna Petronic-Rosic, MD; Sarah L. Stein, MD

HISTORY OF PRESENT ILLNESS
The patient is an 11 year old white male seen in dermatology clinic for evaluation of hair loss from the left eyebrow. The patient and his mother described first noticing redness and a swollen appearance of the left eyebrow region approximately 3 months prior to presentation, which progressed to notably decreased hair in the eyebrow. Prior treatment for presumed alopecia areata with desonide 0.05% ointment twice a day to the affected area for six weeks had not been beneficial. A subsequent 30-day course of oral terbinafine for possible tinea facei also did not resolve symptoms.

PAST MEDICAL HISTORY
Atopic dermatitis

FAMILY HISTORY
Psoriasis and non-melanoma skin cancer (basal cell cancer and squamous cell cancer).

MEDICATIONS
None

ALLERGIES
No known drug allergies.

PHYSICAL EXAMINATION
Involving the left lateral eyebrow was a solitary, well-defined, oval, hypopigmented plaque composed of grouped follicular hyperkeratotic papules and markedly decreased density of eyebrow hairs. The rest of the skin exam was unremarkable. There was no lymphadenopathy.

DERMATOPATHOLOGY
Punch biopsy from the plaque revealed focal parakeratosis, mild acanthosis and spongiosis of the epidermis. Within the follicular epidermis there was abundant mucin and a surrounding peri-follicular lymphocytic infiltrate. There were focal collections of mucin within the hair follicle. The mucin was highlighted by colloidal iron staining. The periodic acid-Schiff stain did not reveal fungal elements.

LABORATORY DATA
Fungal culture of skin scraping: negative

DIAGNOSIS
Follicular mucinosis

TREATMENT AND COURSE
The patient was treated with clobetasol 0.05% cream twice a day for four weeks. Follow up verbal report from the family confirmed excellent response to treatment with regrowth of the eyebrow hair. However, since discontinuing treatment, the patient's mother reports intermittent recurrence of erythema and "swelling". The family was advised to continue use of clobetasol cream once daily on weekend days only.

DISCUSSION
The first description of this entity was in 1957 by Pinkus who coined the term "alopecia mucinosa" [1] .

Shortly thereafter, in 1959, Jablonska, et al. redescribed the condition and employed the term that is now used more frequently, "follicular mucinosis" (FM)[2] This condition is a rare inflammatory disorder of the hair follicles that results in non-scarring alopecia. It affects both sexes and all age groups.[3] Though considered to be idiopathic, the association with malignancy and inflammatory conditions, and the detection of clonal T-cell populations, may hint at a T-cell etiology.[4] The condition is characterized by follicular degeneration with mucin (hyaluronic acid) deposition in the outer root sheath of the hair follicles and an accompanying inflammatory lymphocytic response.[5] The source of the mucin appears to be the follicular keratinocytes themselves.[6]

FM typically presents clinically as grouped folliculocentric papules within discrete patches of alopecia. Other uncommon presentations have been described, including acneiform eruptions,[9] lichen spinulosis-type eruptions,[10] and urticarial eruptions.[11]

Follicular mucinosis is divided into a primary (idiopathic) form and a secondary form occurring in the setting of inflammation or in association with cutaneous T-cell lymphoma (CTCL).[4] A familial form has also been described.[8] Primary FM is more frequently seen in children and favors involvement of the head, neck and upper extremities, and demonstrates spontaneous resolution within a few years.[12, 2] Secondary FM is characteristically seen in older patients and the lesions tend to be more generalized. Truncal involvement, in addition to involvement of the face and extremities, has been observed. The plaques tend to be larger and portend a protracted clinical course.[3]

Progression of primary FM to CTCL is rarely observed in children, whereas in adults the frequency of progression to CTCL has been reported to range from 9-60%.[12,13] Furthermore, follow up of pediatric patients with FM has shown favorable results. In one study of 31 pediatric patients with FM, after a mean follow-up of 6.2 ± 3.7 years, all patients had complete resolution of their lesions. Even though 12 of these patients met the diagnostic criteria of the International Society of Cutaneous Lymphomas (ISCL) and were classified as having MF, none had progression of their disease and all patients had complete resolution of their lesions as well.[14] In another case series, out of 10 pediatric patients (7 with isolated FM and 3 with associated MF) followed for a mean of 4.9 years, none developed any additional lymphoproliferative conditions.[12] T-cell clonality may be seen in up to 70% of patients (less than 40 years of age) with primary FM, though a mean follow-up of 10 years found no progression to CTCL in this cohort.[16] In light of these favorable findings, some authors have proposed that primary follicular mucinosis in children may be considered, at worst, a low-grade lymphoproliferative disorder.[15] Nevertheless, as case reports of primary FM progressing to CTCL,[12] and FM preceding other lymphoproliferative disorders (such as Hodgkin's lymphoma)[14] have been published, close follow up is advocated.[15] Limited clinical involvement of the lesions and typical histopathological findings support the diagnosis of primary follicular mucinosis in pediatric patients. More extensive involvement of the skin and a more chronic course should alert the clinician to investigate further for concomitant disease.[5]

As most cases of primary FM will spontaneously resolve within 2 years, patients can be counseled and observed clinically. Reported treatments that have been used successfully for FM include topical corticosteroids, topical retinoids, photodynamic therapy and oral minocycline.[12,17,18]

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CASE # 10

PRESENTERS
Carly Roman, MD; Arlene M. Ruiz de Luzuriaga, MD, MPH; Christopher R. Shea, MD

HISTORY OF PRESENT ILLNESS
A 71 year old multiracial (Native American, African-American and Caucasian) woman presented for dermatologic evaluation of a growth that had been present on her back for two years. The lesion was extremely tender to palpation and interrupted her sleep by preventing her from lying supine; pieces would occasionally break off. She had not tried any topical treatments for it.

PAST MEDICAL HISTORY
Hypertension, multinodular goiter s/p resection, gastroesophageal reflux disease, sciatica, osteopenia, asthma, and a remote history of psoriasis

FAMILY HISTORY
Non-contributory

MEDICATIONS
Amlodipine 5 mg daily

ALLERGIES
Cortisone, penicillin, simvastatin

PHYSICAL EXAMINATION
A pedunculated, smooth, pink nodule with a hard 10 cm handle-shaped keratin horn protruded from the left lower back.

DERMATOPATHOLOGY
The lesion was removed by shave excision. Histopathologic analysis was remarkable for a dense hyperkeratosis with focal parakeratosis and hemorrhage overlying a cup-shaped invagination of the epidermis. There was hypogranulosis and acanthosis with trichilemmal keratinization and an epidermal collarette; there was no significant atypia. The periodic acid-Schiff stain was negative for fungi or significant basement membrane thickening, but did highlight material consistent with glycogen in the cytoplasm of keratinocytes in the spinous layer; this staining was abrogated by predigestion with diastase.

DIAGNOSIS
Trichilemmal horn

TREATMENT AND COURSE
The patient has been followed clinically without evidence of recurrence. No further treatment was required.

DISCUSSION
Trichilemmal horn is a very rare neoplasm that clinically presents as a cutaneous horn and is occasionally associated with trichilemmal carcinoma, rather than squamous cell, carcinoma, at the base.[1,2] With the inclusion of our patient, fewer than 40 cases have been reported since the condition was first described by Brownstein in 1979, whose seminal case series of 19 patients over a five-year period demonstrated an incidence of 0.021%.[3] Trichilemmal horns tend to affect older women more than men, at median age of 50-70 years. They are most commonly reported on the upper extremities,

followed by the head, with < 15% of cases arising on the back. They generally do not recur in the absence of malignancy.[4]

Histopathology reveals a plate-like nodule with a prominent basement membrane, extending from the epithelium into the dermis.[4,5] The affected epidermis is acanthotic and composed of pale-staining keratinocytes, with pronounced orthokeratotic hyperkeratosis.[6] Abrupt trichilemmal (isthmic) keratinization without a granular layer is present in the overlying horn and within areas of focal parakeratosis. Typically, dermal inflammation is absent.[4,6] Trichemilemmal keratinization normally occurs in the outer root sheath (ORS) of the hair follicle, so this condition is considered to be derived from or differentiating toward the ORS. This notion has been supported by studies demonstrating positive CD34 immunostaining in these neoplasms.[6]

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CASE # 11

PRESENTERS

Adena E. Rosenblatt, MD, PhD; Arlene Ruiz De Luzuriaga, MD; Aisha Sethi, MD

HISTORY OF PRESENT ILLNESS

A 63 year-old Caucasian male with a history of Type II DM, hypertension, hyperlipidemia, peripheral neuropathy and peripheral artery disease was evaluated by dermatology for a 3 week history of erythematous to violaceous nodules that were rapidly increasing in size and number on his trunk, extremities, and head. On admission, the patient was also found to have fevers, malaise, diarrhea, and respiratory distress. A non-contrast CT of the chest showed ground glass opacities in the lung. Patient had an elevated creatinine of 3.9 but renal ultrasound did not show any abnormalities. The patient did not have any recent travel history or sick contacts.

PAST MEDICAL HISTORY

Type II Diabetes on Metformin and Glimepiride
Hypertension on Lotrel
Peripheral artery disease
Hyperlipidemia on Simvastatin and Fenofibrate
Peripheral neuropathy on Gabapentin
Smoker- 1pack/day for 40yrs

FAMILY HISTORY

Non-contributory

MEDICATIONS

Azithromycin 500mg IV daily
Cefepime 1g IV q12hr
Esomeprazole 40mg IV daily
Heparin SQ 5000U q8hr
Furosemide 80mg IV q12hr
Ipatropium 500mcg q4hr
Metronidazole 500mg IV q8hr
Insulin SQ

ALLERGIES

Benadryl

PHYSICAL EXAMINATION

A 63 year old Caucasian male on oxygen by nasal cannula with multiple scattered erythematous to violaceous firm nodules and plaques some with overlying erosion and hemorrhagic crust on scalp, face, trunk, neck and extremities.

DERMATOPATHOLOGY

Diffuse atypical lymphoid infiltrate filling the dermis and extending deeply to the reticular dermis forming nodular collections and involving some foci of adipocytes. The infiltrate consists of medium-large sized lymphocytes with nuclear enlargement and irregularity with few scattered mitotic figures obscuring the dermal-epidermal junction. Epidermotropism and infiltration of the arrector pili muscle is noted. Anti CD2/CD3/CD5 antibodies highlight the majority of lymphocytes. Anti-CD7 antibody highlights ~60% of lymphocytes. Anti-CD4 antibody highlights ~40% of lymphocytes. Anti-CD8 antibody highlights ~60% of lymphocytes. Anti-CD30 antibody does not highlight any of the

lymphocytes. Anti-CD20 antibody highlights scattered cells. Anti-gamma/delta TCR antibody highlights 85-90% of the lymphocytes. Anti-alpha/beta TCR antibody highlights 10-15% of lymphocytes.

LABORATORY DATA

Complete blood count: Leukocytes 5.8 K/µL (3.5-11), hemoglobin 11.7 g/dL (13.5-17.5), platelets 186 K/µL (150-450)
Glucose 188 mg/dL (60-109), Sodium 135 mEq/L (134-149), Potassium 3.8 mEq/L (3.5-5.0), Chloride 101 mEq/L (95-108), BUN 65 mg/dL (7-20), Creatinine 4.4 mg/dL (0.5-1.4)
Total protein 5.2 g/dL (6.0-8.3), Albumin 2.4 g/dL (3.5-5.0), Total bilirubin 0.2 mg/dL (0.1-1.0), Conjugated bilirubin 0.1 mg/dL (0.0-0.3), Unconjugated bilirubin 0.1 mg/dL (0.1-1.0), Serum Alkaline Phosphatase 87 U/L (50-150), AST 58 U/L (8-37), ALT 27 U/L (8-35), LDH 1121 U/L (116-245), Uric acid 7.2 mg/dL (2.0-8.0),
Histoplasmosis, Aspergillus, and Blastomycosis Ag, HIV, Hep B surface Ag were negative
Bone Marrow Biopsy 10/8/13: normocellular bone marrow with trilineage hematopoiesis and granulocytic expansion

IMAGING

PET Scan 10/8/13: hypermetabolic lymph nodes in the neck, chest, abdomen, and pelvis as well as hypermetabolic lesions in the liver and spleen

DIAGNOSIS

Cutaneous gamma-delta T-cell lymphoma

TREATMENT AND COURSE

Patient was started on treatment with Cytoxan and prednisone for 2 days and then was transitioned to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy. Skin lesions improved with CHOP chemotherapy but chemotherapy was complicated by tumor lysis syndrome and patient was started on allopurinol. One week after starting chemotherapy patient developed neutropenic fever that progressed to sepsis. He was diagnosed with mitral valve endocarditis and progressed to develop kidney failure, respiratory failure, and septic brain emboli. Patient died one week after developing neutropenic fever.

DISCUSSION

Cutaneous gamma Delta T-Cell lymphoma (CGDTCL) is rare and accounts for <1% of all cutaneous lymphoid neoplasms. It was incorporated as a definitive entity into the World Health Organization classification of lymphomas in 2008. 5% of normal T-cells express the gamma delta receptor. Gamma delta T-cells play an important role with the innate immune system and are essential for regulation of inflammation, tumor surveillance, wound healing and epidermal integrity. CGDTCL has been associated with lymphoproliferative disorders (ie Hodgkin and non-Hodgkin B-cell lymphoma, CLL), solid neoplasms, hepatitis C, and Hashimoto thyroiditis.

Disseminated deep and indurated plaques and ulceronecrotic nodules characterize CGDTCL. Less commonly patients may have a solitary lesion or localized lesions and the prognosis is similar to generalized presentations. Some patients present with erythematous thin scaly plaques with overlying erosions. These patients tend to have a more indolent course and better prognosis. The most common sites of involvement are the legs followed by the torso and arms. Patients may present with constitutional symptoms such as fever and weight loss. Mucosal involvement may present as ulcerated tumors or aphthous stomatitis. Nodal and extranodal involvement can occur but it is rare. There are reports of testicular, pulmonary, thyroid, breast, nasopharynx, GI, and central nervous system

involvement.

Three histologic patterns can be present in CGDTCL and include epidermotropic, dermal, and subcutaneous. All of these patterns can sometimes be seen in the same lesion. Most cases have a dense atypical lymphocytic infiltrate that may involve the epidermis, dermis, and subcutaneous tissue. A lichenoid or vacuolar interface with variable epidermitropism may occur as well as extravasated red blood cells and scattered necrotic keratinocytes. There may be variable acanthosis and hyperkeratosis. A subset of cases have a predominately panniculitic pattern that is associated with a worse prognosis. Most commonly, CGDTCL is positive for CD3, CD56, gamma M1, granzyme B, TIA-1 but negative for CD4, CD8, CD7, CD5, BF1. However, there are some cases of CGDTCL that may be CD8, CD4, CD5, or CD7 positive. CD8 positivity is more commonly observed compared to CD4. TIA-1 and CD5 are associated with overall mortality.

CGDTCL is very aggressive and often fatal with a mean 5 year survival of ~10-20% and a median disease free survival time of about 15 months. CGDTCL is resistant to many chemotherapies including CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like therapy. Treatment with allogeneic hematopoietic stem cell transplantation has been reported to be effective but mortality remains high. There are also reports of effective treatment of patch or scaly thin plaque lesions with a combination of methotrexate and narrowband UVB.

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CASE # 12

PRESENTERS
Min Deng, MD; Christopher R. Shea, MD

HISTORY OF PRESENT ILLNESS
A 59-year old Caucasian male with a T1N2b base of tongue squamous cell carcinoma presented to our in-patient consult team for evaluation of a prominent erythematous-violaceous rash on the face and dorsal hands. He had been admitted for routine clinical monitoring while undergoing his first cycle of chemotherapy (paclitaxel, 5-fluorouracil, and hydroxyurea) and concurrent targeted radiation therapy. Approximately 2 days after the initiation of his chemotherapy regimen, our patient reported a prominent red rash with associated swelling and tightness of the face that "felt like a sunburn" which had progressively worsened over the subsequent day and spread to include his ears and dorsal hands.

He denied any history of significant recent sun exposure but reported that he typically burns easily and had numerous sunburns, including blistering sunburns, predominantly on his face during childhood. His most recent sunburn was a year prior to presentation and the weather had been overcast during the week of his admission.

He denied any new medications besides his chemotherapy regimen but had previously tolerated low-dose paclitaxel induction therapy without cutaneous side effects. His rash extended well beyond his radiation field, which was limited to the neck and lower facial region.

PAST MEDICAL HISTORY
Hypertension
Numerous sunburns, including blistering sunburns, predominantly on his face during childhood

FAMILY HISTORY
No family history of skin cancers

MEDICATIONS
5-Fluorouracil 1,300mg per protocol
Hydroxyurea 500mg per protocol
Paclitaxel 216mg per protocol
Aspirin 81mg qd
Duloxetine 30mg qd
Furosemide 20mg qd
Omeprazole 20mg qd
Rampiril 10mg qd

ALLERGIES
No known drug allergies

PHYSICAL EXAMINATION
On exam, erythematous-violaceous blanchable patches with mild underlying edema were visible on the sun-exposed regions of the face, ears, and dorsal hands with well-demarcated cut-offs along the submental chin and the dorsal-ventral border of his hands bilaterally.

DIAGNOSIS
Photo-recall dermatitis

TREATMENT AND COURSE

Based on the distribution of his dermatitis on sun-exposed skin surfaces and the clinical history of preceding systemic chemotherapy treatment, we diagnosed our patient with a photo-recall dermatitis. We recommended symptomatic treatment with Triamcinolone 0.1% ointment in addition to sun avoidance and photo-protection with a sunscreen containing titanium dioxide and zinc oxide. Our patient reported improvement of his rash over the following few weeks without the need to reduce his chemotherapy treatment dose. Upon subsequent cycles of chemotherapy treatment he reported significantly milder flares which resolved with Triamcinolone 0.1% ointment.

DISCUSSION

Photo-recall dermatitis is an idiopathic drug-induced reaction on areas of prior UV-induced solar erythema which occurs following systemic administration of a triggering medication. Also referred to as ultraviolet recall dermatitis, ultraviolet enhancement, sunburn recall, and photodermatitis reactivation, this is a rare phenomenon which is most commonly associated with methotrexate. Rare reports of photo-recall dermatitis have been reported in response to chemotherapeutics and antibiotics, including taxanes, gemcitabine, etoposide, cyclophosphamide, suramin, piperacillin, tobramycin, ciprofloxacin, gentamicin, and cefazolin.[1-3]

While our patient received systemic paclitaxel, 5-fluorouracil, and hydroxyurea concurrently, we suspect our patient's reaction was triggered by paclitaxel. There are two prior reports in the primary literature of photo-recall dermatitis occurring following the administration of a systemic taxane; one case occurred following docetaxel administration and the second case occurred following paclitaxel administration.[3,4] While our patient had previously tolerated low-dose paclitaxel induction therapy without side effect, we hypothesize there may be a dose-related threshold for this idiosyncratic reaction.

In a review of 22 cases of photo-recall dermatitis, preceding UV-induced solar erythema occurred from weeks to months prior to administration of the triggering medication.[1] Following the triggering medication, the cutaneous eruption typically occurs within a day to a week and is more intense than the preceding UV insult.[1,3,4]

Treatment is symptomatic with sun avoidance, sunscreen application, and topical and/or systemic corticosteroids. In the prior case report of paclitaxel-induced photo-recall dermatitis, the patient had similar episodes after each infusion of paclitaxel.[4] Our patient reported progressively milder reactions with subsequent same-dose infusions which were well-tolerated with topical corticosteroids.

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CASE # 13

PRESENTERS
Sogyong Auh MD, PhD, Arlene Ruiz de Luzuriaga MD, MPH, and Sarah L. Stein MD

HISTORY OF PRESENT ILLNESS
A 6-year-old girl presented with a pruritic rash on the left arm. It had initially appeared one year ago and was gradually enlarging. The patient had treated the area with triamcinolone 0.1% ointment up to three times daily with minimal improvement. No other family members were affected and there were no pets in the home.

PAST MEDICAL HISTORY
Asthma

FAMILY HISTORY
Noncontributory

MEDICATIONS
Albuterol

ALLERGIES
None

PHYSICAL EXAMINATION
The medial surface of the left upper arm demonstrated grouped red-brown raised coalescing papules with a smooth surface without epidermal change. The rest of the skin exam was unremarkable.

DERMATOPATHOLOGY
A 4-mm punch biopsy from the left medial arm showed hyperkeratosis and focal basal vacuolization. The dermis demonstrated a dense diffuse infiltrate of predominantly lymphoid cells, immunoblasts, and numerous plasma cells. A few mitotic figures were noted. Within the dermis were prominent vessels with slightly plump endothelial cells. Immunohistochemical stains demonstrated anti-CD3 antibody immunolabeling of 70% of the lymphoid cells in the infiltrate. Anti-CD-5 and anti-CD-7 antibodies immunolabeled the same cell population. Anti-CD4 antibody immunolabled 66% of the lymphoid cells while 34% were labeled by anti-CD-8 antibody. Anti-CD30 antibody immunolabeled less than 10% of the lymphoid cells and anti-CD20 antibody immunolabeled 30% of the lymphoid cells. The anti-T.pallidum antibody stain was negative.

LABORATORY DATA
Complete blood count with differential and comprehensive metabolic panel were within normal limits.

DIAGNOSIS
Cutaneous lymphoid hyperplasia consistent with Acral Pseudolymphomatous Angiokeratoma of Children (APACHE)

TREATMENT AND COURSE
The patient was started on mometasone 0.1% ointment twice daily and family noted flattening of lesions and improvement in erythema. Pruritus also improved. Given significant improvement after 1 month, the frequency of mometasone ointment was decreased to twice daily on weekends only.

DISCUSSION

Acral Pseudolymphomatous Angiokeratoma of Children (APACHE) is a rare benign, cutaneous disease. First described by Ramsay *et al.*,[1] five cases were reported in children ranging from 2 to 13 years of age. The entity was described as a unilateral eruption of multiple violaceous-erythematous papules, affecting a foot in four cases and a hand in one case. The lesions were clinically suggestive of angiokeratomas and were asymptomatic. Histology demonstrated epidermal hyperkeratosis and a dense lymphoid infiltrate throughout the dermis. Conspicuous dilated thick-walled blood vessels lined with prominent plump endothelial cells were noted. The infiltrate contained lymphocytes, plasma cells, and histiocytes, but no eosinophils. The original report stressed the importance of recognizing this entity as benign, despite the florid pseudolymphomatous infiltrate. The inclusion of angiokeratoma in the name refers to the clinical presentation, not the histological features. Kaddu *et al.*[2] described 2 cases of APACHE in a 16-year-old boy and a 64-year-old woman. Although the histopathological and immunohistological features were consistent with APACHE, the case of the older woman was distinctive for adult onset and the presentation of a solitary red-brown papule on the back. Therefore the suggestion was made to change the name to "small papular pseudolymphoma" and categorize APACHE in the spectrum of cutaneous pseudolymphomas. However, the original nomenclature has persisted. Since then, approximately 25 cases have been reported in the literature.[2-15] The polyclonality of the inflammatory infiltrate has been demonstrated by polymerase chain reaction (PCR), suggesting a reactional process.[4, 11]

Given the rarity of this entity, no standards regarding treatment exist. In the original report, one patient was treated with curettage, and lesions did not recur. Two untreated patients were followed for 1 and 2 years, respectively, without change in the lesions. A fourth patient was followed for 16 years with gradual flattening of lesions; repeat biopsy demonstrated milder but persistent infiltrate.[1] Topical and intralesional injections of corticosteroids and carbon dioxide laser have been described to flatten lesions, though eventual recurrence of papules was noted.[6, 8] Although the lesions are considered benign, some authors recommend total excision of lesions [8, 10] with no recurrence reported.[6]

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CASE # 14A

PRESENTERS

Mara G. Beveridge, MD; Diana Bolotin, MD, PhD; Sheryl Hoyer, MD; Vesna Petronic-Rosic, MD, MSc; Christopher R. Shea, MD; Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS

The patient is a 67-year-old African-American male who presented with a one-year history of a sore on the right parietal scalp. He believed it had started as a nick from his barber; it had not responded to hydrogen peroxide, witch hazel, Neosporin, or hydrocortisone. An outside provider had prescribed oral cephalexin and griseofulvin, also without improvement.

On initial presentation to dermatology, a 5x5 cm boggy, pink, well-defined plaque with clean borders, yellowish scale, hemorrhagic crust, and associated alopecia was present on the right parietal scalp. Two 1-cm soft, pink, eroded plaques with hemorrhagic crust were present, one behind each ear. A punch biopsy specimen showed extensive surface parakeratosis and neutrophilic crust and a dense perivascular and perifollicular dermal infiltrate of lymphocytes, eosinophils, and numerous plasma cells. Intrafollicular collections of neutrophils and perifollicular fibrosis were present. The periodic acid-Schiff stain was negative for fungi or significant basement membrane thickening. The methenamine silver stain was negative for fungi. The pathological findings were consistent with folliculitis decalvans. Clobetasol 0.05% ointment was prescribed and the patient missed the subsequent follow-up appointment.

The patient returned to clinic seven months later and reported that he had used clobetasol ointment for one month with initial improvement. He now notes itchy blisters in the affected areas on the scalp and behind the ears in addition to newly affected areas on forehead, neck, and upper chest.

PAST MEDICAL HISTORY

Colon cancer (T3N2Mx adenocarcinoma status-post surgical resection in 2004 and adjuvant therapy with 5-fluorouracil and leucovorin with poor follow-up), hypertension, hyperlipidemia, chronic kidney disease

FAMILY HISTORY

Non-contributory

MEDICATIONS

Hydrochlorothiazide, metoprolol, losartan, amlodipine, atorvastatin, aspirin

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

5x5 cm bright pink plaque with focal areas of erosion, yellowish scale, and hemorrhagic crust on the right parietal scalp with associated alopecia. Several tense blisters in bilateral post-auricular spaces at edges of soft pink plaques with overlying erosions and hemorrhagic crust.

DERMATOPATHOLOGY

A subepidermal cleft has numerous eosinophils and neutrophils within the blister cavity and a perivascular and interstitial lymphocytic infiltrate admixed with eosinophils and neutrophils in the superficial dermis. Direct immunofluorescence studies demonstrate linear deposition of IgG and C3 at the epidermal basement membrane zone. Serum indirect immunofluorescence studies are negative.

LABORATORY DATA

Complete blood count with differential: Within normal limits.

Complete metabolic panel: Blood urea nitrogen 21 mg/dL (7-20), creatinine 1.5 mg/dL (0.5-1.4), glomerular filtration rate estimate (calculated, adjusted for African American race) 57 mL/min/BSA (>59). The rest was within normal limits.

G-6PD: 10.6 U/g (8.8-13.4)

Thiopurine methyltransferase: 6.5 U/mL (>15 normal, 10.1-14.9 low normal, 6.0-10.0 carrier, <6.0 deficient)

IMAGING

CT chest, abdomen, pelvis with contrast: New intraluminal mass of the superior left bladder wall suspicious for neoplasm. Further characterization with cystoscopy is recommended in the appropriate clinical scenario. New hepatic lesion in segment 5 suspicious for metastatic disease. Unchanged peritoneal nodule in the right lower quadrant. Findings discussed directly with medical oncologist.

DIAGNOSIS

Cicatricial pemphigoid, Brunsting-Perry type likely paraneoplastic

TREATMENT AND COURSE

At the same time that this dermatologic diagnosis was being made, the patient was independently diagnosed with high-grade papillary urothelial carcinoma and a hepatic metastasis of colonic adenocarcinoma. In consultation with his oncologist and due to active malignancies, systemic immunosuppressants for his cicatricial pemphigoid were initially avoided. The patient began treatment with niacinamide 500mg three times daily, doxycycline 100mg twice daily, and clobetasol 0.05% ointment topical while undergoing treatment for associated malignancies with stabilization of his skin findings. Ophthalmology evaluation showed no evidence of ocular disease.

He underwent transurethral resection of the bladder tumor (TURBT) followed by 6 treatments of intravesical BCG therapy; recurrence of his disease was noted 6 weeks later on routine surveillance cystoscopy. The patient then underwent a repeat TURBT, another complete course of intravesical BDG, and is currently maintained on intravesical gemcitabine with good response. Liver resection was performed for metastastatic colonic adenocarcinoma. The patient received clearance from his oncologist and urologist to begin immunosuppressive therapy; however, at his dermatology clinic follow up, a dramatic improvement in his skin lesions was noted with no new blisters or erythematous plaques and only several remaining small healing crusted plaques. He remains on his current treatment regimen with close follow up.

CASE # 14B

PRESENTERS
Mara G. Beveridge, MD; Diana Bolotin, MD, PhD; Sheryl Hoyer, MD; Vesna Petronic-Rosic, MD, MSc; Christopher R. Shea, MD; Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS
The patient is a 60-year-old African-American female presenting with itchy rash on the scalp for 2-3 months. She was initially diagnosed with seborrheic dermatitis and then tinea capitis by her primary care doctor and was treated with ketoconazole 2% shampoo, fluocinolone oil, clobetasol ointment, and griseofulvin orally, with no improvement.

PAST MEDICAL HISTORY
Hypertension

FAMILY HISTORY
Breast cancer in sister and maternal aunt.

MEDICATIONS
Griseofulvin, ketoconazole 2% shampoo, carvedilol, lisinopril, aripiprazole, duloxetine, cyclobenzaprine, hydrocodone-acetaminophen, nystatin ointment

ALLERGIES
Sulfa

PHYSICAL EXAMINATION
Diffuse and ill-defined patches of erythema and speckled hyper- and hypo-pigmentation with some adherent yellow-brown scale over crown. There is associated hair-thinning and hair-loss with decrease density of follicular ostia.

DERMATOPATHOLOGY
There is a subepidermal blister with a mixed inflammatory cell infiltrate including numerous neutrophils and a few eosinophils. There is diffuse dermal fibrosis. Direct immunofluorescence studies demonstrate linear deposition of IgG, IgM, and fibrinogen in the top of the dermis; the epidermis is absent from this preparation.

LABORATORY DATA
Complete blood count with differential: Within normal limits.
Complete metabolic panel: Within normal limits
G-6PD: 4.7 U/g (8.8-13.4)
Thiopurine methyltransferase: 14.5 U/mL (>15 normal, 10.1-14.9 low normal, 6.0-10.0 carrier, <6.0 deficient)

DIAGNOSIS
Cicatricial pemphigoid, Brunsting-Perry type

TREATMENT AND COURSE
The patient was started on prednisone 40mg daily (0.5mg/kg/day) and, due to her low-normal thiopurine methyltransferase level, azathioprine 50mg daily and continues to use clobetasol 0.05% ointment topically. After four months of therapy, her azathioprine was increased to twice-daily dosing and she could decrease her prednisone dose to 30mg daily. Her disease is stable with no new areas of

involvement. She was also started on alendronate 35mg weekly, in anticipation of long-term use of systemic corticosteroids.

DISCUSSION

Cicatricial pemphigoid is a rare, automimmune, subepithelial, blistering disorder. It differs from bullous pemphigoid (BP) in that it has a predilection to affect mucosae, heal with scarring, and have a more chronic course. It is associated with tissue-bound and, less often, circulating autoantibodies directed at bullous pemphigoid antigen 180 (i.e., BP 180, BPAG2, type XVII collagen) and laminin 332 (i.e., laminin 5, epiligrin). Histopathologically, cicatrical pemphigoid is very similar to BP, demonstrating a subepidermal or subepithelial split with eosinophils and spongiosis; older lesions of cicatricial pemphigoid can show dermal fibrosis, differentiating it from BP.

Likewise, direct immunofluorescence findings in the two entities are similar, with both demonstrating linear deposition of IgG (predominantly IgG4 and IgG1) and C3 along the subepithelial basement membrane zone; linear deposits of IgA and IgM occur less commonly. Under indirect immunofluorescence, BP and most cases of cicatricial pemphigoid have antibodies that localize to the epidermal roof, whereas patients with anti-laminin 332 cicatricial pemphigoid have antibodies that bind to the dermal side. Antibody titers are generally very low, though some authors have suggested that patients with higher titers and both IgG and IgA circulating autoantibodies have more severe disease.

BP as a paraneoplastic phenomenon has been described; specifically, the anti-epiligrin subtype, is reported with large-cell carcinoma of the bronchus, adenocarcinoma of the lung (in a patient with HIV infection), endometrial carcinoma, gastric carcinoma, and now our patient A with urothelial carcinoma. These associations must be interpreted with caution since BP typically affects patients aged 60-80 years old who have an inherently increased risk of malignancy. Certain authors have suggested that the clinical course of BP does not necessarily follow closely that of the associated malignancy, thus failing the criteria for paraneoplasia as suggested by Curth; however, when the anti-epiligrin subtype of cicatricial pemphigoid is separated from other types of BP there does appear to be a parallel course between the severity of the dermatosis and the activity of the malignancy, as reported by Fukushima et al. While testing for anti-epiligrin antibodies was not performed in our patient A, his cicatricial pemphigoid did improve significantly when his urothelial carcinoma was under better control.

Additionally, laminin 332 has been reported in pulmonary, gastrointestinal, and urothelial epithelia and the inflammation and subsequent release and exposure of the antigen could hypothetically trigger a secondary autoimmune response. Specifically, a recent study on paraffin-embedded tissue collected from 35 patients with invasive urothelial cell carcinoma demonstrated an association between laminin 332 expression and increased invasion of bladder cancer cells. Another study comparing paraffin-embedded specimens from both invasive and non-invasive urothelial cancer patients found an increased risk of death associated with increased laminin 332 loss from the basement membrane and an increase of cellular retention of laminin 332; a multivariate analysis showed that the increase of cellular retention of laminin 332 was the most important prognostic parameter. These studies confirm a role of laminin 332 in both cicatricial pemphigoid and invasive urothelial carcinoma; however, the exact interplay between the two remains unclear.

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