Chicago Dermatological Society

October 2021 - *Online* Educational Conference

Program & Speaker Information
CME Certification
Case Presentations

Wednesday, October 13, 2021
Online

UI Health | UIC

Conference Host
Department of Dermatology
University of Illinois at Chicago
Chicago, Illinois

Program

Host: University of Illinois at Chicago
Wednesday, October 13, 2021
Online Conference

8:30 a.m.	**Sign-in and Member Visitation Time**
9:00 a.m.	**Welcome & Introduction** *Jordan Carqueville, MD - CDS President*
9:05 a.m. - 9:50 a.m.	***Guest Lecture*** "Photodynamic Therapy, Field Cancerization Therapies and Energy Based Devices" *Nellie Konnikov, MD*
9:50 a.m. - 10:00 a.m.	**Questions & Answers**
10:00 a.m. - 11:00 a.m.	**Resident Case Presentations & Discussion** *UIC Residents*
11:00 a.m. - 11:45 a.m.	***Guest Lecture*** "Dermatologic Care in the V.A Health System: Observations or the Years and Lessons Learned" *Nellie Konnikov, MD*
11:45 a.m. - 11:55 a.m.	**Questions & Answers**
11:55 a.m. - 12:00 p.m.	**Closing Remarks and Announcements** *Jordan Carqueville, MD*
12:00 p.m.	**Meeting adjourns**

Mark the Date!

Next CDS meeting will be virtual on Wednesday, November 10th – Co-hosted by Northwestern
Watch for details on the CDS website: www.ChicagoDerm.org

Guest Speaker

NELLIE KONNIKOV, MD

Clinical Professor of Dermatology, Boston University School of Medicine; Chief of Dermatology at the Boston VA Medical Center
Boston, MA

Nellie Konnikov, MD is Clinical Professor of Dermatology at Boston University School of Medicine and Chief of Dermatology at the Boston VA Medical Center. She earned her medical degree from the Moscow Medical School. Following an internship at Brigham and Women's Hospital in Boston, she completed her dermatology residency at Boston University/Tufts University Combined Residency Program (1985 - 1987), where she also was chief resident. Dr. Konnikov also was a Dermatology Foundation Research Fellow, Department of Internal Medicine and Immunology at the New England Medical Center (1986-87).

Dr. Konnikov holds several faculty appointments, including Clinical Professor of Dermatology at Tufts University School of Medicine, Lecturer at Harvard Medical School, Professor of Clinical Dermatology at Boston University School of Medicine. She is the chief of the Dermatology Section at the VA Boston Medical Center, a position she has held since 2002.

Committee service includes numerous positions at the local, regional, national and international levels. Dr. Konnikov has received a number of honors throughout her career and has numerous publication credits to her name.

CME Information

October 13, 2021

Overview

The Chicago Dermatological Society was established in 1901 and has strived to provide meaningful educational opportunities to dermatologists in the Chicago area for more than a century. Guest speakers from across the country share their expertise with CDS members, as well as residents in training medical students doing their dermatology rotation. CDS schedules six day-long meetings each year which are "hosted" by one of the dermatology residency programs in the city. Two lectures are given by the guest speaker, and the residents of the host institution present cases which are offered for audience discussion. During the coronavirus pandemic, CDS has continued to organize our regular educational conferences, but these are providing in a somewhat shorter “virtual” setting.

Target Audience

This activity has been designed to meet the educational needs of dermatologists. CDS members, residents in training and medical students engaged in their dermatology rotation are invited to attend.

Learning Objectives

At the conclusion of this meeting, the participant should be able to:

1. Describe the basic principles of energy-based devices, such as lasers, and their application in treating dermatologic conditions.
2. Discuss the goals of field cancerization treatment, including in the context of reducing the risk of developing keratinocyte carcinoma.
3. Explain the means by which photodynamic therapy is utilized in dermatology.
4. Described the factors a clinician should consider when selecting the appropriate therapy when using energy-based devices and photodynamic therapy for treatment of a dermatological condition.
5. Discuss management of dermatology patients withing the VA health care system, the challenges confronting physicians, and the development of care within the system over a number of years.

Physician Accreditation Statement

This activity is planned and implemented by Indiana Academy of Ophthalmology (IAO) and the Chicago Dermatological Society. IAO is accredited by the Indiana State Medical Association to provide continuing education for physicians.

Credit Designation for Physicians – IAO designates this live activity for a maximum of 3 *AMA PRA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Attendees are required to submit a CME claim form in order to receive credit. Each attendee eligible for CME credit will receive a link to an online claim for and an evaluation form. Thank you for your attention to this important item.

Disclosure of Conflicts of Interest

The IAO and CDS require instructors, planners, managers and other individuals and their spouse/life partner who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by IAO and CDS for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All speakers are asked to follow the "first slide" rule to repeat their conflict of interest disclosures during their talk. None of the participants in this conference have disclosed any relevant potential conflicts of interest.

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Contact Information

For information about the physician accreditation of this program please contact the CDS administrative office at: 847-680-1666; email: Rich@RichardPaulAssociates.com

Americans with Disabilities Act

In compliance with the Americans with Disabilities Act, we will make every reasonable effort to accommodate your request. For any special requests, contact CDS at: Rich@RichardPaulAssociates.com

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed in this activity should not be used by clinicians without evaluation of patient conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Dislosure of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. The planners of this activity do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of the planners. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

UNIVERSITY OF ILLINOIS
COLLEGE OF MEDICINE

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Case #1

Case Presented by Christy Waterman, MD and Roger Haber, MD

History of Present Illness:
A 17-year-old African American female presented to an outside dermatologist with a three-year history of recurrent painful bullae on the hands, feet, and chest as well as erosions on the oral mucosa and lips. The initial episode was accompanied by a fever. The patient endorsed blister formation within 2-3 days following any contact with nickel. She reported needing to avoid touching school lockers, metal on clothing, and even the metal poles on buses and pool ladders. Painful targetoid blisters formed in areas of direct contact with nickel, and also in areas without direct contact. Initial biopsy was suggestive of erythema multiforme, but there was no improvement with valacyclovir. Treatment with oral prednisone improved her symptoms but discontinuation resulted in flares.

Past Medical History:
The patient has no significant past medical history

Medications:
None

Allergies:
No known drug allergies

Family History:
None

Social History:
None

Review of Systems:
The patient endorsed painful oral erosions and painful bullae on the hands, feet and chest.
The patient denied fever, chills, arthralgias, cough, vision changes, GI/GU symptoms

Physical Examination:
The patient has multiple firm targetoid bullae on the lateral fingers, bilateral palms, dorsal feet, chest, and left lateral arm. She also has tender erosions on the orolabial and buccal mucosa.

Laboratory Data/Diagnostic Procedures and Tests:
The following were positive or abnormal:
CBC with Hgb 10.9 g/dL (11.1-15.9)
Platelets 524 thousand/µL (130-450)
ESR elevated to 42 mm/hr (0-20)
Patch testing with TRUE test: 2++ "Strong Positive" reaction to nickel sulfate

The following were negative or within normal limits:
CMP, TSH/free T4, HSV 1 and HSV 2 IgG and IgM, ANA, Anti-dsDNA, Anti-DNase B strep antibody, hepatitis B cAb/sAg/sAb, hepatitis C antibody, Quantiferon Gold, T. pallidum antibodies.

Histopathology:

Right palm, skin: Acute interface dermatitis with basal vacuolization, superficial lymphocytic perivascular infiltrate, and necrotic keratinocytes consistent with EM.

Left palm, skin: Interface inflammation with intraepidermal cytoids favoring EM. DIF negative for autoimmune blistering disorder, with lichenoid tissue reaction.

Diagnosis:
Nickel-Associated Recurrent Erythema Multiforme

Treatment and Course:
The patient was started on valacyclovir 500 mg daily, a 2-week prednisone taper, triamcinolone 0.1% ointment, and was counseled to avoid nickel. She continued to experience intermittent outbreaks of targetoid lesions on the lips, hands, and extremities approximately every other month. She was then treated with class I topical corticosteroids, oral valacyclovir 1g daily, nystatin swish and spit, oral fluconazole, and several additional oral prednisone tapers with minimal improvement. Methotrexate 10mg daily was initiated along with folic acid and 40mg of intramuscular triamcinolone, but methotrexate was self-discontinued 2 weeks later when the patient experienced a recurrence of her cutaneous symptoms.

In our facility, an additional biopsy was obtained, and was consistent with EM. Dapsone was avoided due to the patient's chronic anemia. The patient was started on mycophenolate mofetil 500mg twice daily and a prednisone taper.

Discussion:
Erythema multiforme (EM) is an acute, immune-mediated condition characterized by the abrupt onset of numerous symmetric cutaneous, fixed red macules that progress over 24 to 72 hours to form distinctive targetoid lesions on the skin. EM minor has either mild or no mucosal involvement and no systemic symptoms, while EM major has severe mucosal involvement and systemic symptoms including fever and arthralgias. Mucosal involvement typically involves oral sites more often than ocular or genital sites. An estimated 90% of EM cases are caused by infection. HSV 1/2 are the most common triggers, with infection typically preceding EM by 1 to 3 weeks. Other infectious etiologies include mycoplasma pneumonia, histoplasma capsulatum, vulvovaginal candidiasis, and Hepatitis C virus. Non-infectious causes include NSAIDs, sulfonamides, antiepileptics, TNF-alpha inhibitors, radiation therapy, menses, immunization, polymorphic light eruption, and connective tissue disease.

Recurrent EM is a rare variant that causes significant morbidity. While it is historically associated with HSV infection, the majority of cases are idiopathic. Our patient associated her EM outbreaks with any contact to her known contact allergen of nickel. There have been a handful of reports of EM in association with contact sensitivities to tropical wood, natural rubber latex, poison ivy, and benzoic acid in food products. It has been noted that EM in these cases may occur with or without an eczematous component of acute allergic contact dermatitis.

Histologically, EM is characterized by acute vacuolar interface dermatitis with individual necrotic keratinocytes above the basal layer, moderately dense superficial dermal perivascular lymphohistiocytic infiltrate, and absent or rare eosinophils. Most cases of EM self-resolve without sequelae within 2 weeks. The exception is EM major with severe mucosal involvement, which may persist for 6 weeks and can lead to ocular complications. First line treatment is symptom-based with topical corticosteroids and analgesics. For severe cases, systemic prednisone or immunosuppressants play a role. Antiviral prophylaxis with acyclovir, valacyclovir or famcyclovir recommended to reduce frequency and duration of HSV outbreaks.

Our patient with recurrent and persistent erythema multiforme did not respond to typical treatment with valacyclovir and prednisone. She was recently started on mycophenolate mofetil, with azathioprine as another secondary option if she fails mycophenolate mofetil. Additional therapeutic options for recurrent EM include cyclosporine, dapsone, anti-TNF alpha therapies, and IV Immunoglobulin G.

Essential Lesson:

- Recurrent EM is uncommon and is typically idiopathic or associated with HSV infection, for which suppressive antiviral therapy may be helpful.
- In cases of recurrent EM, other rare causes such as contact allergens should be considered.

References:

1. Huff JC, et al. Erythema multiforme: a critical review of characteristics, diagnostic criteria, and causes. *J Am Acad Dermatol*;1983:8:763-775.
2. Wetter DA, et al. Recurrent erythema multiforme: Clinical characteristics, etiologic associations, and treatment in a series of 48 patients at Mayo Clinic, 2000 to 2007. J Am Acad Dermatol;2010,62:1:45-53.
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Case #2

Case Presented by Priyanka Patel, MD and Sheryl Hoyer, MD

UNKNOWN

An 85-year-old male presented to the dermatology clinic with a several week history of a rapidly enlarging mass on the right upper arm with surrounding erythema and associated pain.

Case #3

Case Presented by Victoria Kuritza, MD and Sheryl Hoyer, MD

History of Present Illness:
A 76 year old female presented to tele-dermatology visit with a greater than 10 year history of recurring blisters. Recently she experienced flares affecting her mouth, face, back, neck, and groin. She noted these blisters rupture easily, releasing clear pink fluid. She recalled a particular flare on her back after a knee surgery several years ago. At that time, she saw an outside dermatologist who diagnosed her with bullous pemphigoid. She was given a steroid ointment and 10 mg oral prednisone every other day, and the flare resolved. The patient continued to experience waxing and waning of blisters, with an increase in flaring noted since 2019.

Past Medical History:
Chronic lymphocytic leukemia (stable, no treatment), recurrent herpes simplex virus, hypertension, type II diabetes mellitus

Medications:
Prednisone 2.5 mg/day, amlodipine, verapamil, atenolol, metformin, furosemide, tramadol, aspirin, calcium supplementation

Allergies:
No known drug allergies

Social History:
No tobacco, alcohol, or illicit drug use

Review of Systems:
The patient endorsed oral erosions and blisters on her body. She denied any fevers, chills, night sweats, weight loss, or joint pains.

Physical Examination:
Photos provided by the patient during initial tele-visits show eroded lesions, others with crusting over eroded base, and on her back are multiple small crusty lesions with a few larger crusted erosions. No oral erosions are seen.

Laboratory Data/Diagnostic Procedures and Tests:
IgG BMZ antibody titer: 1:2560, dermal localization
Salt-split skin substrate titer: 1:1280
IgG Collagen VII antibodies: 71 (H)

Histopathology:
Right Breast: Acute subepidermal bulla with moderate neutrophilic infiltrate

Diagnosis:
Inflammatory Epidermolysis Bullosa Acquisita

Treatment and Course:
During the above work-up, the patient's blistering became more diffuse, involving her arms, hands, chest, back and feet. She denied any blisters in the mouth/genitals, though they were present in the past flares. She had self-increased her prednisone to 10 mg/daily, as that helped

in the past. She was started on doxycycline 100 mg PO BID for its anti-inflammatory effect, and her prednisone was increased to 20 mg/day. Now improved, she has been slowly tapering off the prednisone, and is now taking 7.5mg daily. She was further started on colchicine 0.6mg daily. Due to her CLL, hematology and oncology are involved to decide on the most appropriate treatment.

Discussion:

Epidermolysis Bullosa Acquisita (EBA), a rare acquired mucocutaneous autoimmune blistering disorder, results from antibody production to the NC1 domain of type VII collagen. Type VII collagen is a major component of anchoring fibrils which span the lamina densa and sublamina densa. Autoantibodies are most commonly IgG, though other variants have been described with IgA autoantibodies. Clinically, vesicles and bullae are observed on the skin, as well as mucous membrane erosions.

Several distinct forms of EBA exist, with the two major types including the classical/mechanobullous and the inflammatory, or nonmechanobullous forms. Classical EBA presents with non-inflammatory bullae and erosions on the hands, feet, elbows, and knees, as well as mucous membranes - areas where repeated microtrauma are most common. More severe cases can result in scarring of the digits, mitten deformity, nail loss, alopecia, and esophageal stenosis. Milia are also often observed in scarred areas. Inflammatory EBA tends to present with vesicles and bullae on the trunk, flexural, and intertriginous areas that do not necessarily heal with milia or scarring. In addition to resembling bullous pemphigoid, inflammatory EBA may less commonly resemble other autoimmune bullous disorders such as mucous membrane pemphigoid and IgA bullous dermatosis. Mucosal involvement has been reported in approximately ⅕ of patients with EBA, with oral lesions being most common. Ocular, genital, esophageal, tracheal/laryngeal, and anal lesions have also been reported.

The International Bullous Disease Group (IBDG) reached agreement that routine histological, direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) findings observed in EBA may be indistinguishable from other immunobullous disorders. Histopathological findings include subepidermal blister formation with varying degrees of inflammatory infiltrate.

The IBDG recommends the following ideal scenario for diagnosis: 1) clinical findings compatible with EBA, 2) subepidermal blister formation on histology, 3) DIF microscopy positive for a linear immune deposit pattern along the dermal-epidermal junction (DEJ), and 4) Enzyme-linked immunosorbent assays (ELISA) demonstrating Type VII collagen targeting by autoantibodies.

Should ELISA be unavailable, another serologic test demonstrating autoantibodies against collagen VII can be substituted. These include a positive IIF and immunoblot or negative IIF on collagen VII deficient skin.

If the patient is seronegative to collagen VII antibodies, a few other tests can support the clinical findings and DIF deposits. These include u-serrated pattern on DIF, direct immune electron microscopy (IEM) demonstrating immune deposits at the anchoring fibril zone, or fluorescence overlay antigen mapping (FOAM) demonstrating immune deposits below collagen 7.

Finally, as the above tests are more limited to academic centers, DIF and/or IIF on salt-split skin can be performed, though it is necessary to rule out anti-laminin-332 and p200 pemphigoid by testing for their autoantibodies.

Because EBA is very rare, currently there are no randomized control trials to evaluate for and establish a gold-standard treatment. EBA is notoriously refractory to treatment, including prednisone. Trauma avoidance, sun protection and appropriate wound healing measures are advised for all patients. Colchicine and dapsone can be used for their anti-neutrophilic benefit, and efficacy has also been noted with regular IVIG, high dose cyclosporine, azathioprine, rituximab, and photopheresis. This case is presented to highlight the diagnostic challenge of EBA and importance of further exploration with randomized controlled trials.

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6. Komori T, et al. Efficacy of intravenous immunoglobulins for the treatment of mucous membrane pemphigoid-like epidermolysis bullosa acquisita. *Eur J Dermatol*. 2017;27(5):563-564.
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Case #4

Case Presented by Neha Chandan MD, Sheryl Hoyer MD and Michelle Bain MD

Patient 1

History of Present Illness:
A fifteen-year-old Hispanic boy presented with a two-year history of a rash on the face, scalp, chest, stomach, back, and arms. The patient endorsed itching and blisters evolving to brown papules and plaques that became generalized. He reported having biopsies done in Mexico and Peoria, IL which he was told were consistent with seborrheic keratoses and seborrheic dermatitis, respectively. The patient tried various over-the-counter and prescription creams, including mupirocin, topical steroids, crisaborole, ketoconazole 2% shampoo, and intralesional triamcinolone injections with no improvement.

Past Medical History:
Normal newborn hearing exam
Hearing loss at age 4 requiring bilateral hearing aids at age 6
Tentative diagnosis of Pendred Syndrome without confirmatory genetic testing
Fatty Liver Disease
Migraines

Medications:
Topiramate

Allergies:
No known drug allergies

Family History:
Sister with horseshoe kidney and irregular menses
Consanguineous maternal grandparents

Review of Systems:
The patient endorsed pruritus and blisters. He denied mucosal involvement, fevers, chills, or joint pains.

Physical Examination:
The patient has enumerable hyperpigmented brown macules, papules and plaques scattered diffusely over the face, neck, upper extremities, and trunk.

Laboratory Data/Diagnostic Procedures and Tests:
None

Histopathology:
Skin, left back: Acantholytic dyskeratosis, consistent with Darier's Disease

Diagnosis:
Darier’s Disease

Treatment and Course:

Treatment with oral retinoids was discussed due to the widespread distribution of lesions, but given the patient's history of fatty liver disease, topical therapy initiated. The patient was initially treated with triamcinolone 0.1% ointment once daily to the affected areas on the body and tacrolimus 0.1% ointment once daily to the affected areas on the face. It was also recommended that the patient apply tretinoin 0.1% cream to affected areas on the face and body nightly. The scalp was treated with ketoconazole 2% shampoo and fluocinonide 0.05% solution daily. The patient was referred to genetics for ATP2A2 testing and SLC26A4 testing for Pendred syndrome. The patient was subsequently lost to follow up.

Patient 2

History of Present Illness:
A twenty-five-year-old Caucasian female presented with a ten-year history of an intermittent itchy rash on her right upper arm and right upper back. The rash recurred one to three times per year, typically in the summer. Each episode lasted approximately three weeks, and began as small, itchy bumps that progressed to vesicles. Following excoriation, the vesicles would drain clear fluid and bleed before crusting over. The rash always recurred in the same locations. The patient endorsed worsening of the rash with heat and exercise.

Past Medical History:
Acne, untreated

Medications:
None

Allergies:
No known drug allergies

Family History:
Mother with a chronic, diffuse erythematous rash of unknown diagnosis. Patient no longer in contact with mother.

Review of Systems:
The patient denied any mucosal lesions, fevers, chills, or joint pains.

Physical Examination:
The patient has pink to tan scaly papules in a linear blaschkoid configuration on the right posterior upper arm.

Laboratory Data/Diagnostic Procedures and Tests:
None

Histopathology:
Skin, right upper arm: Intraepidermal acantholytic dyskeratosis

Diagnosis:
Type 1 Segmental Darier's Disease

Treatment and Course:

After discussing topical and systemic retinoids the patient was initiated on tretinoin 0.05% cream nightly to affected areas. The patient is scheduled to follow up in 3 months.

Discussion

Darier's Disease, also known as keratosis follicularis, is a rare genetic disorder with a prevalence of approximately 1:100,000 people. Darer's disease is due to ATP2A2 gene mutation coding for the SarcoEndoplasmic Reticulum Calcium-ATPase (SERCA) pump, which regulates cytosolic $Ca2+$ concentration. This pump is also associated with the function of cytokeratin and desmosome proteins, thus mutations lead to defective keratinocyte intercellular adhesions. Typical onset is during early adolescence to mid-adult life, with a peak in the second decade prior to puberty.

Darier's disease is typically inherited in an autosomal dominant fashion with clinical presentations in a seborrheic distribution. Approximately 10% of cases occur in a localized distribution as a result of somatic mosaicism. Mosaicism occurs after fertilization, as such there is a very low chance of inheriting a localized form unless gonadal cells are affected. Localized Darier's disease can present as several variants including unilateral, linear, segmental, and zosteriform. Unlike generalized Darier's disease, localized disease has a later onset, appearing during the third or fourth decade of life. Two phenotypes of segmental Darier's disease exist. In type 1, a postzygotic mutation causes a mosaic pattern of skin involvement with normal surrounding skin. In type 2, additional postzygotic mutations occur in other alleles of ATP2A2, leading to loss of heterozygosity and manifesting as linear streaks overlying a background of generalized Darier's disease.

Darier's disease is often diagnosed based on clinical presentation and family history. Classic cutaneous findings include reddish-brown wart-like or hyperkeratotic papules that coalesce into greasy plaques. Lesions may be painful, pruritic, or malodorous. Additional manifestations include cobble stoning of the oral mucosa, vertical red and white nail bands, palmoplantar pits, and acrokeratosis verruciformis-like papules. Histologically, it is not possible to differentiate between the variants of Darier's disease. Typical findings include papillomatous epidermal hyperplasia and intraepidermal acantholytic dyskeratosis. Classic dyskeratotic cells include corp ronds, most often found in the spinous layer, and grains, most often found in the stratum corneum.

Classic Darier's disease has a chronic course with frequent exacerbations resulting in significant morbidity. Treatment for all types includes avoidance of triggers and daily use of sunblock and emollients. Systemic retinoids including isotretinoin (starting dose 0.5 mg/kg/day in 2 divided doses) and acitretin (starting dose of 10-25 mg daily) are the most effective treatment, but are limited by their side effect profile. Topical retinoids and medium-potency topical corticosteroids are utilized in localized variants. Additional therapeutic options include keratolytic agents such as salicylic acid and lactic acid. Pulsed dye, carbon dioxide, and erbium:YAG lasers have shown success in recalcitrant disease.

Essential Lesson:

- Type 1 Segmental Darier's Disease is a rare, localized form caused by post-zygotic mosaicism.
- In Type 1 Segmental Darier's Disease, the lesions are distributed in a linear pattern, following the lines of Blaschko.
- Systemic retinoids are first-line treatment for classic Darier's Disease while topical therapies are sufficient for localized variants.

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Case # 5

Case Presented by Carolina Puyana MD and Roger Haber MD

History of Present Illness:

A 64-year-old female presented with a pruritic nodule on her scalp. She first noticed the lesion one year prior to presentation. She stated that the lesion had slowly been increasing in size and that it easily bled upon minor trauma. She denied pain or purulent discharge. She denied any personal or family history of skin cancer.

Past Medical History:
Hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, cataracts, lung nodules, latent tuberculosis

Medications:
Carvedilol, losartan, warfarin

Allergies:
No known drug allergies

Social History:
No history of tobacco, alcohol, or drug use

Review of Systems:
The patient denied any fevers, chills, night sweats, or weight loss.

Physical Examination:
On the vertex scalp is a 12x12mm friable exophytic nodule with reddish appearance. There is no cervical, occipital, supraclavicular, or axillary lymphadenopathy.

Laboratory Data/Diagnostic Procedures and Tests:
PET/CT examination of skull to mid-thigh level: no abnormal uptake.

Histopathology:
Scalp, skin: Sections demonstrate a nodulocystic proliferation of epithelial cells with cellular polymorphism, including clear cells, secretory cells, basaloid cells, and focal mucinous/goblet like cells. The tumor cells show focal nuclear pleomorphism and scattered mitotic figures. Luminal formation is present. There are collections of eosinophilic basement membrane material within the tumor. There is focal ulceration and focal invasion identified at the periphery of the tumor.

The overall findings mostly represent an atypical clear cell hidradenoma. The presence of nuclear pleomorphism, scattered mitotic figures, focal invasion, and focal tumor necrosis raises a possibility of hidradenocarcinoma (malignant clear cell hidradenoma).

Diagnosis:
Hidradenocarcinoma (HAC)

Treatment and Course:
The patient underwent Mohs surgery, requiring a total of two Mohs stages to completely clear the tumor of any atypical cells. The surgical defect was reconstructed with a bilateral advancement

flap. Sutures were removed two weeks later as the site was healing well. The patient was then scheduled for a total body skin exam in three months.

Discussion:

Hidradenocarcinoma (HAC; also known as malignant acrospiroma or malignant nodular hidradenoma) is a rare malignant adnexal tumor of eccrine and apocrine derivation. The head and neck are the most common sites of presentation. HAC arises most commonly in the sixth and seventh decades of life. It is a very aggressive tumor characterized by high frequency of locoregional recurrence and distant metastases. HAC lacks a distinctive clinical appearance, mimicking a variety of benign adnexal lesions. It commonly arises de-novo and presents as an individual, firm nodule, sometimes with an ulcerated reddish appearance, as in the case of our patient.

HACs are difficult to distinguish histologically from hidradenomas (HAs), their benign counterpart. On histology, HAs consist of well circumscribed, large tumor nodules occupying the entire dermis with focal epidermal connections. Classically, there is evidence of scattered sweat ducts within the tumor nodules and prominent dermal sclerosis with keloidal collagen. Although HAs are predominantly nodular they may also present with large areas of cystic spaces. HAs are comprised of three main cell types: squamoid cells, poroid cells, and clear cells. Any of these cell types may predominate. Histologic criteria used to distinguish HACs from HAs include nuclear pleomorphism, atypical mitoses, comedo-like necrosis, hemorrhage, infiltrative borders, and lymphovascular or perineural invasion. The presence of tumor cords with peripheral invasion may be used as a sole-criteria for the diagnosis of HAC. In our case, although the overall findings mostly represented an atypical HA, the presence of focal peripheral invasion along with several atypical features as above suggests a diagnosis of HAC.

The treatment of choice for HA is complete surgical excision to assure that the tumor is truly HA and not HAC lacking cytologic atypia, as such variants may only be recognized by infiltration into surrounding tissue. Traditional histologic methods of determining tumor margins may miss tentacle like projections of tumor cells in unexamined sections, since only a percentage of tumor margin is examined. Because of the rarity of HAC and the variation in presentation, no consensus about the treatment protocol for the management of HAC exists today. Traditionally, HAC has been managed with wide local excision with recurrence and metastatic rates up to 20-50%. More recently, Mohs surgery is advocated to be the preferred treatment not only for HAC but also HA because it allows for systematic evaluation of 100% of the tumor margin. A Mayo Clinic study showed that in an average of 1.5 stages, Mohs surgery led to complete clearance of HAC with zero recurrences and metastases in a 7 year follow up period. In our patient, 2 Mohs stages where required for clearance.

Like the treatment of other skin carcinomas, adjuvant therapy is based on grade, margin positivity, angiolymphatic invasion, and metastasis; however, no consensus exists yet for adjuvant treatment for HAC. The utility of sentinel lymph node biopsy (SLNB) remains the subject of debate. Some recommend SLNB to detect subclinical metastases. Radiation therapy is used selectively in patients when tumor is unresectable, for incomplete primary surgery, or for improving local control in the setting of lymph node involvement. The efficacy of adjuvant chemotherapy has not been demonstrated widely but it plays a role in the metastatic setting. Agents reported in the literature include 5-fluorouracil, capecitabine, doxorubicin, platins, cyclophosphamide, vincristine, and bleomycin. Targeted therapies including trastuzumab, EGFR inhibitors, PD-1 inhibitors, and PI3K/Akt/mTOR pathway inhibitors are under current investigation. In our patient there was no lymphadenopathy and tumor margins were cleared with surgery, therefore adjuvant therapies were not pursued.

Essential Lesson:

- Histologic criteria used to distinguish HACs from HAs include nuclear pleomorphism, atypical mitoses, comedo-like necrosis, hemorrhage, infiltrative borders, and lymphovascular or perineural invasion.
- Mohs surgery is the preferred treatment for HAC because it allows for systematic evaluation of 100% of the tumor margin.

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Case #6

Case Presented by Stephanie Kuschel, MD and Carlotta Hill, MD

History of Present Illness:
A 34-year-old man presented with a two-year history of alopecia, madarosis, and thickening of the skin on his forehead, nose, and earlobes. The patient also had a one-year history of erythematous, scaling patches on his arms, legs, and back. One month prior to presentation, the patient had a biopsy at an outside hospital that was consistent with lepromatous leprosy. He was then referred to the UIC Hansen's Disease Clinic for further evaluation and treatment.

Past Medical History:
Anemia, unspecified

Medications:
None

Allergies:
No known drug allergies

Family History:
The patient has a brother in Mexico who has similar symptoms of hair loss on his scalp, eyebrows, and eyelashes. No other family members have symptoms of Hansen's disease or another skin condition.

Social History:
The patient grew up in Michoacán, Mexico as a farmer. The patient reports there are many armadillos wild in this area of Mexico, but he denied close contact with them. The patient is not married, and he does not have any children. He denies any use of tobacco, alcohol, or illicit drugs.

Review of Systems:
The patient denied fevers, chills, weight loss, and pain. He denied paresthesia in his hands or feet.

Physical Examination:
The patient has several erythematous, slightly indurated, scaling plaques and patches on his bilateral shins, right mid-back, and bilateral dorsal forearms. The patient has thinning of his bilateral eyebrows, especially of the lateral two-thirds, and loss of his eyelashes. He has thickening of the skin of his forehead, glabella, and bilateral earlobes. The patient has diffuse hair thinning throughout his scalp, most prominent at the crown. He has loss of protective sensation in his right distal hallux and the medial instep of his left foot. Eye closure is intact, and there is no conjunctival hyperemia.

Laboratory Data:
The following lab was abnormal:
Hemoglobin 11.2 gm/dL(13.5-17.5)

The following were negative or within normal limits:
Chest X-ray; Urine analysis; C-reactive protein; Hepatitis B Surface Antigen; Hepatitis C Antibody; Hepatitis B Surface Antibody; Hepatitis B core IgM; Helminth Antibody; Strongyloides Antibody;

QuantiFERON-TB Gold; Glucose-6-phosphate Dehydrogenase; Antinuclear Antibodies with reflex; Comprehensive Metabolic Panel; and the remainder of the Complete Blood Cell count.

Histopathology:
Skin, left forearm: Perivascular histiocytic infiltrate consistent with lepromatous leprosy. There are moderately dense perivascular and periadnexal histiocytic infiltrates. Fite stain highlights numerous bacilli within the histiocytes.
Molecular studies: Positive polymerase chain reaction (PCR) for *Mycobacterium lepromatosis*

Diagnosis:
Multibacillary Leprosy with *M. lepromatosis*

Treatment and Course:
At the patient's initial visit a repeat punch biopsy was taken of the patient's right earlobe and sent to the National Hansen's Disease Center for histology and PCR. Additionally, physical and occupational therapy teams evaluated the patient and noted minor abnormalities in the patient's sensory exam as described above. The preliminary biopsy report from the National Hansen's Disease Center detected *Mycobacterium lepromatosis* via PCR. The patient refused clofazimine treatment and as substitute therapy was started on dapsone 100mg daily, rifampin 600mg monthly, and minocycline 100mg nightly. The patient missed his next monthly follow-up visit, and was off minocycline and dapsone for the interim. Repeat lab testing revealed a significant drop in his Hemoglobin to 9.9 gm/dL. The patient also expressed difficulty obtaining routine lab monitoring; consequently, an alternate treatment plan was offered consisting of monthly dosages of moxifloxacin 400mg, rifampin 600mg, and minocycline 100mg. The patient continues to do well with the current treatment regimen following several months of treatment. His anemia is improving (Hg 11.5 gm/dL), and he has noticed increased hair growth on his extremities as well as fading of his skin lesions.

Discussion:
Leprosy (also known as Hansen's disease) is an infectious disease caused by two genetically distinct species of acid-fast bacilli (AFB), *M. leprae* and *M. lepromatosis.* M. lepromatosis is a strain of Mycobacterium discovered in 2008, and so far, cases have been reported in Canada, Asia, and Central and South America. *M. lepromatosis* may be associated with more aggressive forms of Hansen's disease, including several cases of diffuse lepromatous leprosy (DLL), which manifests as diffuse skin involvement without nodules. On the face this is typified by a striking loss of the eyebrows and eyelashes (madarosis). DLL lesions may progress to ulcers and the rare, potentially fatal, immune hypersensitivity reaction Lucio's phenomenon, in which bacilli infiltrate endothelial cells leading to ischemic epidermal necrosis, ulcers, and potentially catastrophic injury. Both bacterial strains of the Myocobacterium leprae complex respond well, but slowly, to multi-drug therapy (MDT) and are curable.

Leprosy demonstrates a predilection for the skin, peripheral nerves, and reticuloendothelial system, and untreated disease can lead to severe morbidity including permanent nerve damage leading to sensory loss, muscle paralysis, disfigurement, and/or blindness. Diagnosis of leprosy primarily relies on identification of the clinical findings, which may be supported by a slit-skin (SS) smear to estimate the number of AFB present, reported as the bacterial index (BI). In the United States, where diagnostic costs are less prohibitive, skin biopsy and PCR studies are most commonly used in diagnosis. In fact, the biopsy finding of AFB invasion of the nerves is pathognomonic for leprosy and considered the gold standard of diagnosis.

Lepromatous leprosy is characterized by many hyper or hypopigmented red to violaceous macules and patches, which may progress to plaques and nodules. Diffuse facial skin involvement can lead to leonine facies with thickened skin and madarosis. In countries where leprosy is now rare, a high index of suspicious is needed to detect the disease, and it should be considered whenever anesthesia is noted in hypopigmented or erythematous lesions.

Two main classification systems exist, including the Ridley-Jopling classification system and the World Health Organization (WHO) classification system. The WHO separates leprosy into either Paucibacillary (PB) or Multibacillary (MB) disease, with MB disease including any patient with more than five skin lesions and PB disease including any patient with five or less skin lesions. A positive SS smear, regardless of the number of lesions, is considered MB disease. The Ridley-Jopling diagnostic classification system uses a combination of clinical and histologic features with the BI to stratify leprosy on a spectrum that ranges from tuberculoid leprosy at one end and lepromatous leprosy at the other. The clinical and diagnostic features of each of these categories correlate with the host immune response, with a more robust Th1 immune response correlating with less severe disease at the tuberculoid end of the spectrum, and a weak Th1 response at the lepromatous end of the spectrum.

The WHO and the National Hansen's Disease Program (NHDP) have outlined multi-drug therapies (MDT) for leprosy in an effort to limit resistance and improve efficacy. The WHO recommends treatment of PB for six months with rifampicin 600mg/month, dapsone 100mg/day, and clofazimine 300 mg/month and 50mg/day. For MB leprosy, the same regimen is recommended for 12 months. The NHDP recommends a longer course of treatment, effectively doubling the length of treatment for PB and MB and includes daily doses of rifampicin 600mg (rather than monthly doses). The NHDP also excludes clofazimine in treatment of PB leprosy and excludes the monthly dose of clofazimine in MB leprosy. The NHDP has recommendations regarding alternate treatment regimens that may be pursued in patients with contraindications or side effects or drug-resistant leprosy. For instance, minocycline 100mg daily can replace dapsone or clofazimine.

MDT has proven highly effective with low rates of relapse; however, treatment failures due to medication noncompliance and adverse side effect profiles (like the distressing red-brown skin pigmentation caused by clofazimine) illustrate the need for more alternative regimens. Monthly doses of rifampin, ofloxacin, and minocycline (ROM) for MB leprosy for 24 months demonstrated similar efficacy clinically and histologically as compared to 24 months of treatment with rifampicin, dapsone and clofazimine. The demonstration of moxifloxacin as the most powerful known fluoroquinolone against M. leprae (with activity similar as that of rifampin) has led to a new proposed monthly treatment protocol consisting of rifampin 600mg, moxifloxacin 400mg, and minocycline 100mg (RMM). This alternative regimen is supported by leaders in the NHDP due to its more favorable side effect profile and better compliance. Further studies and publications on this new protocol regarding its efficacy are on-going. However, due to the higher cost of this treatment protocol, adoption by the WHO is unlikely.

Herein we present a case of multibacillary leprosy associated with infection with M. lepromatosis, a more recently discovered strain of mycobacteria, and treatment with an alternate MDT regimen.

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Case #7

Case Presented by Brian Cahn, MD and Roger Haber, MD

History of Present Illness

A 35-year-old man presented with multiple pigmented papules/nodules on his face and scalp. He has had many similar papules/nodules over the past twenty years which have been treated at outside institutions with excision, curettage and electrodessication, topical 5-Fluoruarcil, topical imiquimod, topical ingenol mebutate, topical tretinoin and photodynamic therapy. He has also had multiple epidermal inclusion cysts excised. He has had genetic testing at an outside institution that was "positive for mutation", but is unsure of the specific gene. He also has had an echocardiogram which was normal. He avoids the sun and uses sun protection. He has not seen a dermatologist in at least four years and is interest in discussing treatment options in the context of wanting to start having children in the near future.

Past Medical History

Basal cell carcinomas, odontogenic keratocysts, chalazions requiring excision, strabismus requiring surgical correction

Medications

None

Allergies

None

Family history

No history of skin conditions or autoimmune conditions. No family history of skin cancer and other cancers.

Review of Systems

No chest pain, dyspnea, dizziness, diplopia, vision changes, headaches, nausea or vomiting.

Physical examination

Scalp: At least 50 pigmented papules. Dermoscopy with ovoid nests, pigmented borders, arborizing branch-like telangiectasias and areas of focal ulceration.
Face: Medial right lower eyelid with a 1 cm pigmented exophytic papule. Numerous pigmented papules across forehead and temples.
Upper extremities: Bilateral palms with scattered 1mm keratotic pits
Lower extremities: Bilateral medial thighs each with one 1.8x2cm and 2.1x2cm cystic nodule. Lateral left knee with one 1.4x1.8cm cystic nodule. Hyperkeratosis of soles

Histopathology

Scalp, skin: Numerous nests of basaloid cells extending from the epidermal-dermal junction into the underlying dermis. These nests exhibit retraction spaces and peripheral palisading consistent with pigmented nodular basal cell carcinoma:

Diagnosis

Basal Cell Nevus Syndrome (Also known as Gorlin-Golz syndrome)

Treatment and Course

The right eyelid papule was removed urgently by oculoplastic for concern for lower punctum

obliteration, and the pathology revealed basal cell carcinoma (BCC) as expected. Due to the extensive number of BBCs on the scalp and face, surgical excision of all lesions was deemed impractical as well has not desired by the patient. The patient stated a preference to avoid restarting topical treatments and photodynamic therapy for concern that these did not help in the past. Initiating vismodegib was discussed at length but was placed on hold as patient is planning to have children soon. The patient was started on pulse itraconazole 100 mg BID for 4 weeks, and two lesions that intermittently bled were shaved off for patient comfort. Of note, scalp lesions did not change in size after the 4 weeks of itraconazole. The patient was referred to genetics for counseling on autosomal dominant disease and his desire to have children.

Discussion:

Basal cell nevus syndrome (BCNS) is an uncommon autosomal dominant disorder that predisposes individuals to neoplasms and developmental abnormalities. Its prevalence is 1 in 19,000-256,000 and there is no gender predilection. The primary manifestations include multiple basal cell carcinomas (BCCs), odontogenic keratocysts of the jaw, palmoplantar pits, calcification of the falx cerebri and dystrophic ribs. As in our patient the BCCs tend to form in the sun-exposed areas of the head and neck but non-sun-exposed areas are also susceptible. Pigmented BCCs are sometimes misdiagnosed clinically as melanocytic nevi. In their lifetime a patient may have a few BCCs to more than a thousand, and they can develop the first BCC by early childhood. Other cutaneous manifestations include facial milia, palmoplantar hyperkeratosis, epidermoid cysts and basaloid follicular hamartomas. Many patients have distinctive facies with macrocephaly, frontal bossing, a broad nasal root, and hypertelorism.

BCNS is caused by mutations in the hedgehog pathway (HH), which is important in cell-proliferation and differentiation. The most common mutation is in the tumor suppressor gene patched-1 (*PTCH1)*, with less common mutations in *PATCH2* and *SUFU*. The PTCH1 receptor normally suppresses the activation of smoothened (SMO) and hence regulates glioma-associated oncogene (GLI)-related transcription factors. In BCNS, *PTCH1* loss-of-function mutation causes unregulated activation of the HH leading to cell growth and neoplasia.

Diagnostic criteria for BCNS were put forth by Shanley in 1994 with modifications by Kimonis in 1997 and Bree in 2011. Diagnosis is made by fulfilling one major criterion with genetic confirmation, two major criteria, or one major criterion and two minor criteria. Clinically, our patient met three major criteria (>3 BCCs, odontogenic keratocysts, palmar pits) and one minor criteria (ocular abnormalities). Genetic testing should not be relied on alone since it is often unable to detect mutations in all affected individuals. Our patient endorsed previous genetic testing but this could not be confirmed.

Given BCNS's chronic nature, the goal of treatment should be to minimize morbidity associated with the syndrome. Patients should be counseled to use sunscreen frequently and to avoid sunlight to prevent BCCs. The standard for BCC treatment remains surgical excision or Mohs micrographic surgery. However, since patients with BCNS often have numerous BCCs, non-invasive treatments should be utilized as well including cryosurgery, topical imiquimod, topical 5-Fluoruarcil and photodynamic therapy. Radiotherapy is relatively contraindicated because BCNS patients are exceptionally prone to developing BCCs following ionizing radiation. Systemic treatment with HH inhibitors (HPIs) such as vismodegib and sonidegib can be used to treat multiple BCCs in BCNS; however, significant toxicities limit their use as a lifelong treatment. In the pivotal 2012 trial leading to vismodegib's FDA approval, serious adverse events were reported in 25% of patients, most commonly muscle spasms, weight loss, fatigue, and loss of appetite [Sekulic 2012]. More recent studies have looked at the use of topical HPIs for BCCs in BCNS . Systemic itraconazole appears to have HPI activity with small studies demonstrating efficacy for

BCCs. The PD-1 inhibitor Cemiplimab , currently FDA-approved for locally advanced or metastatic BCC, is also under study for BCNS.

Vismodegib is FDA approved for metastatic basal cell carcinoma and for locally advanced basal cell carcinoma that has recurred following surgery or for patients who are not candidates for surgery or radiation. Vismodegib and other HPIs are known to be teratogenic, embryotoxic, and fetotoxic due to the importance of the Hedge Hog pathway in embryogenesis. Vismodegib also carries a boxed warning to advise males of the potential risk of exposure through semen to a pregnant partner or a female partner of reproductive potential. No human studies of vismodegib's effects on male spermatogenesis and fertility have been performed. Male BCNS patients interested in family planning such as our patient must consider the risks and benefits of systemic treatment as well as the potential implications of the syndrome's autosomal dominant inheritance pattern with near complete penetrance but widely variable expressivity. Prenatal diagnosis of BCNS in a pregnancy sired by a man with BCNS has been reported and the parents terminated the pregnancy.

The care of BCNs patients is multidisciplinary and should include clinical geneticists, developmental pediatricians, oral and maxillofacial surgeons, cardiologists, ophthalmologists, gynecologists, neurologists and psychiatrists.

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Case #8

Case Presented by Isabelle Sanchez, MD, MPH and Michelle Bain, MD

History of Present Illness:
A 4-week-old male infant in the neonatal intensive care unit was consulted to dermatology for a rash that began 10 days prior as a diffuse red scaly eruption on the neck, trunk, arms, legs, buttocks, perineum, and face. The skin findings were preceded by bloody mucoid diarrhea for 2 weeks, intermittent episodes of respiratory distress since birth, and failure to thrive. The patient later developed recurrent fevers and was found to have cardiac defects. Initially, the chronic diarrhea was accredited to a milk allergy or bacterial infection, however, the patient failed to improve with dietary modifications and broad-spectrum antimicrobial, antifungal, and antiviral therapies.

Past Medical History:
Cephalohematoma
Chronic diarrhea
Failure to thrive
37 weeks premature delivered by emergent C-section due to placental abruption

Medications:
Ampicillin, gentamicin, nystatin, acyclovir

Allergies:
None

Family History:
The patient's mother had 2 previous miscarriages (during first trimester and at 17 weeks)
Patient's older female sibling required care in the NICU after birth and had a history of chronic diarrhea
Mother had no history of birth defects, intellectual disability/developmental delay, cancer, seizures, hearing loss, sudden cardiac death, or known genetic conditions.

Review of systems:
The patient had recurrent fevers, bloody mucoid diarrhea, intermittent episodes of respiratory distress, and failed to gain weight and thrive.

Physical Examination:
There are numerous erythematous to hyperpigmented papules with collarettes of scale on the neck, trunk, arms, legs, buttocks, perineum, and face. Some areas have an ichthyotic appearance. The palmoplantar surfaces, genitals, and mucosa are spared.

Laboratory Data/ Diagnostic Procedures and Tests:
Hgb 8.6, Platelets 139000
Blood cultures x2 negative
RSV, HSV, and COVID19 negative
Enteroviral PCR negative, stool PCR panel negative for GI pathogens, urine cultures negative

Genetic analysis:
Whole genome sequencing revealed a missense variant 1098G>T, Trp366Cys (substitution of tryptophan to cysteine) in the DNA binding forkhead domain of *FOXP3* gene.
Normal male SNP chromosomal microarray 46XY
Rapid whole genome sequencing identified FOXP3, c.1098G>T, VUS, hemizygous associated with IPEX syndrome
T-cell differentiation: T-regulatory cells 1.1% (range 1.0% - 7.0%), 18 cells/uL (range 8-48 cells/uL)
G6PD pathogenic variants identified
Congenital diarrhea gene panel negative
Acylcarnitine profile normal

Diagnosis:
Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) Syndrome

Treatment and Course:
The patient was initially treated with topical triamcinolone 0.1% ointment twice daily to the affected areas on the body with notable improvement. He then began sirolimus 0.5mg twice daily and methylprednisolone 3 mg/kg/day. The patient was transferred to Northwestern Lurie Children's Hospital for higher level of care for a hematopoietic stem cell transplant from his sister.

Discussion:
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome is a rare genetic disorder that presents within the first year of life with severe diarrhea, dermatitis, and autoimmune endocrine disorders, commonly diabetes mellitus type 1. The pathogenic mutation occurs on the X chromosome in the *FOXP3* gene, thus most patients are males.

FOXP3 controls the production of regulatory T cells (Treg) via encoding the DNA binding protein, the abnormal function of which causes immune cells to attack the body's healthy tissues through failure to suppress T cell activation and proliferation. Subsequently, this results in early autoimmunity in multiple different organ systems that manifest the common findings of enteropathy, diabetes mellitus, and dermatitis. Other associated features may include thyroiditis, nephropathy, hemolytic anemia, thrombocytopenia, recurrent infections, and dermatitis.

Skin findings are frequently associated with IPEX Syndrome, as 50% of reported cases in the literature had associated skin findings and up to 70% among males. Common cutaneous presentations of IPEX syndrome include most commonly eczematous dermatitis, followed by psoriasiform dermatitis, alopecia areata, exfoliative erythroderma, idiopathic urticaria, and bullous pemphigoid.

IPEX syndrome is clinically suspected by its constellation of symptoms and autoimmune conditions. Often, Treg levels can appear normal in affected patients, which may further impede proper diagnosis. Skin biopsy may help rule out other dermatoses but often is nonspecific and variable. Typical biopsy results may identify spongiosis consistent with eczematous dermatitis. Definitive diagnosis requires gene sequencing to identify a mutation in *FOXP3*.

In our patient, the mutation found was not previously reported in the literature. Trp366 stabilizes the hydrophobic core of *FOXP3*'s forkhead domain and is vital for proper function. Computer silico models had previously predicted that the missense variant 1098G>T, Trp366Cys found in our patient had a deleterious effect on protein function, although this variant was labeled as a variant of uncertain significance because the variant was not yet reported in public databases. Thus,

there was insufficient evidence to place it into the likely pathogenic category. However, the patient's family was counseled as if the variant was pathogenic, based on clinical findings and the genetic mutation's effect on protein function. Parental testing was offered to determine if the variant was an inherited or de-novo alteration, however the mother declined further testing.

Unfortunately, without treatment, affected patients typically die from staphylococcal infections and sepsis. Topical corticosteroids are frequently used for treatment and have the best response in improving skin findings in patients with IPEX syndrome. For recalcitrant cases, immunosuppressive therapy has been used with minimal improvement, which has included systemic corticosteroids, tacrolimus, and cyclosporine. Other treatments that have been documented in the literature with variable results are fresh frozen plasma, intravenous immunoglobulin, sirolimus, infliximab, and rituximab. The only definitive treatment for IPEX syndrome cases is an HLA-matched allogenic stem cell transplant, with a survival rate of 81.2%.

Recognizing the constellation of cutaneous findings, systemic symptoms and autoimmune conditions is critical for early diagnosis and treatment. Although this patient had severe systemic features of IPEX syndrome, his cutaneous findings were responsive to topical therapy as the first line of treatment prior to receiving systemic immunomodulators for his systemic findings. We present this case to illustrate the typical clinical presentation of IPEX syndrome, the complexities in arriving at a diagnosis of a rare genetic condition, and to add to the current literature of cutaneous presentations of IPEX syndrome. Finally, this genetic mutation has not been associated with previously documented IPEX syndrome cases in the literature and thus adds to the genetic understanding of this condition and may be a possible associated pathogenic variant in the future.

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