New England Dermatological Society

NEW ENGLAND DERMATOLOGICAL SOCIETY CLINICAL MEETING

Saturday, December 4, 2021

UMass Chan Medical School Department of Dermatology

UMass Chan MEDICAL SCHOOL

FUTURE MEETINGS OF THE NEW ENGLAND DERMATOLOGICAL SOCIETY

February 12, 2022 – Didactic Meeting*
Hosted by:
Boston Children's Hospital
Boston, MA

April 30, 2022 – Clinical Meeting
Hosted By:
Harvard Medical School / Beth Israel Deaconess Medical Center
Boston, MA

October 1, 2022 – Clinical Meeting*
Hosted by
Tufts Medical School
Boston, MA

**meeting format still tbc*

NEW ENGLAND DERMATOLOGICAL SOCIETY

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December 4, 2021

Dear Attendee:

I would like to take this opportunity to invite you to become a member of the New England Dermatological Society (NEDS). A key benefit to membership in the Society is complete and full access to the NEDS website. Such access allows members to search for all uploaded cases presented at past clinical meetings. These cases provide a valuable database of unusual dermatological disorders and their treatment.

The New England Dermatological Society offers a 50% discount on the first year's membership dues for any person who applies within one year of completing their residency or fellowship training. The Society also offers a $50 rebate on membership dues to any member who refers a new member to the Society.

Initiate your application by applying online and then forward your CV and letter of recommendation to our administrator, Gayle Sommer at NEDS@mms.org. You'll find membership application information and materials in the 'Membership' section of www.nederm.org.

If you have any further questions, please contact Gayle at **781-434-7731** or NEDS@mms.org. Your application will be reviewed at the next scheduled Council meeting once all required application information is received.

With best regards,

Avery LaChance, MD, MPH
Secretary, New England Dermatological Society
www.nederm.org

Case of the Year, Century Scholar and Book Awards

Case of the Year

The ***Case of the Year Award*** is given to the best clinical case presented during the academic year. Each program submits their "best" case at the conclusion of each academic year so that the Council can vote and decide on the award recipient. If the winner then presents the case at the American Academy of Dermatology (AAD) in the gross and microscopic session he/she will be awarded $ 500 to help with travel expenses. $ 500 will also be presented to the recipient's residency program's educational fund.

Century Scholar Award

The ***Century Scholar Award*** is given to the dermatology resident or trainee in their dermatology rotation who wrote up the winning case. He or she is awarded a $ 500 Amazon gift card towards the purchase of books.

If the case is accepted for presentation at a conference and the trainee travels to present it, $ 500 is awarded to the trainee to help with travel expenses. Their write up must specify that the case was presented at a New England Dermatological Society Conference and the case must be accepted within two years to receive the travel funding.

Book Award

The New England Dermatological Society will award $ 500 towards the purchase of a medical textbook to any dermatology resident at a member institution who satisfies the following requirements:

1. The resident is a first author of a report based on a case presented at a meeting of the New England Dermatological Society.

2. The report is accepted for publication by a peer-reviewed journal within one year of the meeting and contains language indicating that the "Case was presented at a meeting of the New England Dermatological Society at (institution) on (date)."

3. The resident supplies the Society's Secretary with a copy of the final journal acceptance letter and a receipt for the purchased medical textbook. The Society will then award the recipient with a gift certificate in the amount of $500 towards the purchase of the medical textbook.

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Every physician matters, each patient counts.

IMPORTANT

Conference Evaluation and CME Information

Registered attendees will receive an email within 7-10 business days of this event from nejmcust@mms.org with a link to the online evaluation for this activity.

Once you complete the online evaluation you will receive instructions on how to claim your CME credit and receive your certificate.

For questions on the evaluation or certificates, please contact Customer Service at 800-843-6356 or nejmcust@mms.org.

MASSACHUSETTS MEDICAL SOCIETY

Every physician matters, each patient counts.

Clinical Meeting Hosted by UMass Medical School Dept. of Dermatology / UMass Memorial Hospital

December 4, 2021

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Patrick Mulvaney, MD, MPH	Cambridge Healthcare Research	Consultant
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Acknowledgements

Welcome to the New England Dermatological Society Meeting at the University of Massachusetts Chan Medical School. We are grateful for the exceptional teamwork displayed and support provided by all members of the UMass Department of Dermatology. Without your combined efforts, this meeting would not be possible.

We would like to acknowledge the following contributors:

We would first like to thank our outstanding **Moderators** Jessica St. John MD and Eric E. Morgan, MD. Their leadership helped materialize this phenomenal educational experience, and we are deeply grateful for their commitment to clinical and academic excellence.

Next, we thank our **Guest Speakers** Rita Khodosh, MD PhD**,** Mehdi Rashighi MD, and Julia O. Baltz MD for eloquently delivering their clinical experiences and expertise to the NEDS community.

We also thank the **Faculty** who guided us in the crucial write-up and editing process, offering us their wisdom along the way. They include Mark J. Scharf MD, Nikki A. Levin MD, PhD, Leah T. Belazarian MD, Riley E. McLean-Mandell MD, Bassel H. Mahmoud Abdallah MD, Mehdi Rashighi MD, and Karen Wiss MD. We thank Patrick M. Mulvaney MD who helped carefully craft the presentation as well.

We cannot thank our **Resident Physicians** enough, who served in all aspects of the planning process and were indispensable teammates. They are Steven Krueger MD, Katherine Su MD, Zainab Abbas MD, Vijaya Daniel MD, Isabella Plumptre MD, Mary Awad MD, Heather Gochnauer MD, Elana Putterman MD, and Sarah Servattalab MD.

We next thank our **Dermatopathologists**, who brought their exemplary diagnostic skills, life-long clinical lessons, and passion to this meeting. They are April Deng MD, Patrick O'Donnell DO, and Zendee Rose P. Elaba MD.

We would like to thank our **Administrative Assistants** Maureen LaVigne and Esmeralda Valois for their superlative coordination that made this meeting happen. We also thank Gayle Sommer for her knowledgeable guidance along this path.

We thank the **Interns, Medical Students and DNP Student** who dedicated their time to preparing excellent case write-ups. They include Holly Neale, Kelly Barry, Shauna Rice, Afsheen Sharifzadeh, Kelly Flanagan, Gabriella Paquette, Kyla Pagani, Nicole Loranger, Sina Foroutanjazi, Alec Gramann, Renee Joyce, Emilee Herringshaw, Alice Tan, Isabella DiMare, Lucy Xu, Stephanie Choi, Jack Hanna, Jatin Narang, and Ryan Chen.

Finally, we thank the **Planning Committee** which includes John E. Harris MD PhD, Mary E. Maloney MD, Nikki A. Levin MD PhD, and Leah T. Belazarian MD for their keen oversight every step of the way, along with a special thanks to Karen Wiss MD, **Chief Planner**, for the tireless work and fierce leadership she offers the UMass Dermatology team.

Best wishes from all of us,

Apoorva Trivedi MD
Chief Resident Planner

Table of Contents

CASE 1

A 15-MONTH-OLD BOY BORN WITH COLLODION MEMBRANE AND ERYTHRODERMA

Patient

JL is a 15-month-old Hispanic male.

Presenters

Gabriella Paquette, MSIII
Heather Gochnauer, MD
Leah Belazarian, MD
Karen Wiss, MD

History

An otherwise healthy 15-month-old Hispanic boy was born vaginally at 34 weeks in the setting of preterm premature rupture of membranes (PPROM) with a collodian membrane diagnosed at birth. At 3 weeks of age, he had tight collodion over fingers and toes and potential need of surgical release. The membrane desquamated over the first two months of life, revealing diffuse erythema and plate-like scale which progressed to a mixture of dark plate-like and fine scale without significant erythema.

Pregnancy and Birth History: Spontaneous vaginal delivery at 34 0/7 after uncomplicated pregnancy. 26-day NICU stay complicated by one apneic episode and *Pseudomonas* and *Staph aureus* conjunctivitis treated with ciprofloxacin.

Past Medical History: Infantile hemangioma

Family History: Noncontributory

Allergies: NKDA

Medications: Artificial tears; tretinoin 0.1% cream; pediatric multivitamin

Physical Examination

Day of life 0: Pink, taut, translucent membrane with erythroderma covering body, palms, and solesMembrane was smooth with fissures and bleeding in creases and flexural surfaces. Mild eclabium and bilateral lower lid ectropion. No dysmorphic features, alopecia, blisters, or fingernail changes.

Age 6 weeks: Mild eclabium, improved from prior. Bilateral lower lid ectropion, and erythema with dark brown, plate-like scale across all skin surfaces. Largest scales on face, scalp and distal extremities.

Age 13 months: Bilateral lower lid ectropion with diffuse ichthyosiform scale across scalp, trunk and extremities with large plate-like, light brown scales on lower > upper extremities.

Laboratory Data

- Genetic studies: Homozygous mutation in TGM1gene suggesting autosomal recessive congenital ichthyosis

Treatment

At birth:

- Vaseline to whole body 4x day
- Placement in humidified isolette

Current:

- Bathing 1-2x daily with gentle exfoliation in baking soda bath w/ goal pH of 7.8
- Vaseline to the whole body after bathing and at least 3x daily
- Tretinoin 0.1% cream on eyelids nightly
- Ophthalmology following for ectropion

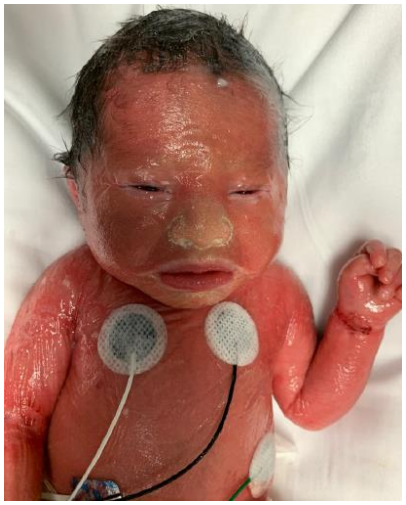

Figure 1. Presentation at birth with collodion membrane and ectropion.

CASE 1

A 15-MONTH-OLD BOY BORN WITH COLLODION MEMBRANE AND ERYTHRODERMA

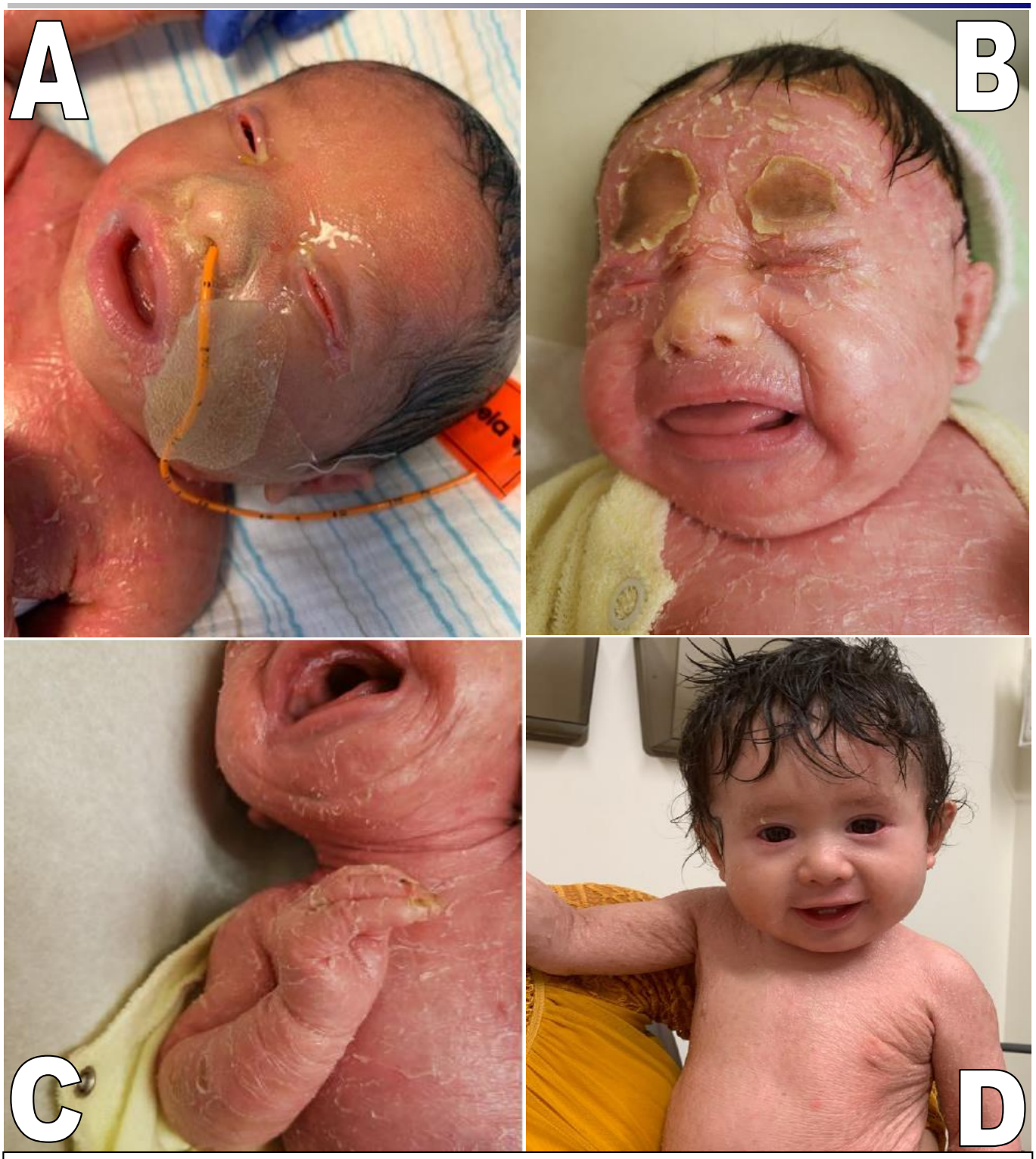

Figure 2. Presentation at birth with collodion membrane and ectropion (A), at 6-weeks-old with bilateral ectropion (B), plate-like scaling, and erythema (B, C), and at 13-months-old with bilateral ectropion and diffuse ichthyosiform scale (D).

LAMELLAR ICHTHYOSIS

Discussion

- Lamellar ichthyosis (LI) is one variant on the continuum of phenotypes classified as autosomal recessive congenital ichthyosis (ARCI). ARCI presents at birth and is caused by errors in keratinization and desquamation of the skin. Phenotypes range from thick, dark, armor-like plates of cornified skin and associated fissures to fine, white scale with underlying erythroderma. LI typically presents at birth with a collodion membrane that desquamates to reveal dark brown plate-like scale without erythema. Associated findings for those more severely affected include ectropion, eclabium, scarring alopecia of the scalp and eyebrows, and palmoplantar keratoderma.
- ARCI is diagnosed clinically ± genetic evaluation, but there are at least 12 genes associated with the condition including: ABCA12, ALOX12B, ALOXE3, CASP14, CERS3, CYP4F22, LIPN, NIPAL4, PNPLA1, SDR9C7, SLC27A4, and TGM1. TGM1 mutations are the most commonly identified genetic variant in those with ARCI without harlequin presentation at birth. Identifying the offending mutation can help predict disease severity and risk of extracutaneous findings.
    - TGM1 codes for the enzyme transglutaminase 1 which is extensively involved in the cross-linking of structural proteins required to establish proper skin barrier function and form a stable, cornified cell envelope in terminal differentiated keratinocytes. Without proper transglutaminase 1 activity, other transglutaminase enzymes cannot form essential cross-linking leading to decreased scaffolding for lipid integration and subsequently thickened plates of hyper-cornified keratinocytes resistant to desquamation.
- Differential diagnosis includes all conditions on the ARCI spectrum including the less severe nonbullous congenital ichthyosiform erythroderma (NBCIE), the self-improving collodion ichthyosis, and the more severe harlequin ichthyosis. Included on the differential for a collodion baby are syndromes such as: Gaucher syndrome, Sjögren-Larsson syndrome, Netherton syndrome, and Keratitis-Ichthyosis-Deafness/KID syndrome.
- LI is a nonsyndromic ARCI and thus mainly affects the skin and cornea and is not associated with conditions involving other organs. Patients with LI have a normal lifespan but may experience complications including poor thermoregulation due to hypohidrosis, limited movement due to thickened scale, secondary infection, and ophthalmologic and otologic issues related to decreased lubrication and scale build up, respectfully.

Teaching Points

- Final clinical diagnosis of an ARCI in a newborn with collodion membrane can only be made after desquamation of collodion membrane reveals underlying clinical features.
- Physicians and parents should monitor the extremities as the collodion sheds to assess for potential compression syndrome of the digits if the tight membrane does not desquamate properly on its own.
- Management of infants with collodion membrane should include temperature monitoring, humidification, emollient use, and close ophthalmology follow-up for complications associated with ectropion such as corneal dryness, irritation, and infection.
- People with LI are treated via symptom management with regular emollient use and topical (e.g., tazarotene or tretinoin) or oral retinoids (e.g., acitretin or isotretinoin) depending on age and severity, along with regular vision and hearing screenings.
- Ichthyotic diseases have an IL-17 dominant immune profile. A case study of secukinumab (anti IL-17) in erythrodermic ichthyosis showed good effect. A clinical trial is currently examining secukinumab treatment in adults with ARCI, epidermolytic ichthyosis and Netherton syndrome.

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CASE 2

A 32-YEAR-OLD WOMAN WITH PROGRESSIVELY HARDENING SKIN

Patient

MS is a 32-year-old woman.

Presenters

Kyla Pagani, MS III
Elana Putterman, MD
Isabella Plumptre, MD
Patrick O'Donnell, DO
Leah Belazarian, MD

History

A 32-year-old-female presented to our clinic for hardening of the skin. She reported a history of gait abnormalities starting in early childhood as she learned to walk. Soon thereafter, she experienced progressive hardening of her skin on the thighs, upper back, and arms, resulting in limited mobility and range of motion. She notes restricted range of motion of her shoulders (R>L) and right hip. Over the course of 3 years, she has had increasingly limited mobility of the right arm.

Past medical history: Hypothyroidism, polycystic ovvarian syndrome, and anxiety

Family history: Hypercholesterolemia, diabetes, a paternal grandmother with breast cancer, and a paternal aunt with colorectal cancer

Allergies: No known allergies

Medications: Levothyroxine, sertraline

Physical Examination

Extensive band-like induration of the right volar forearm extending from the wrist to the right upper arm with rippling of the right posterior upper arm. Hyperpigmented indurated plaques with subtle hypertrichosis on the bilateral upper shoulders, left anterior arm, and right abdomen. The right proximal medial thigh showed induration with rippling and pseudocellulite. No erythema, tenderness, or surrounding lilac border present.

Laboratory Data

- Glucose 112mg/dL *(<100mg/dL*); AST 44U/L (*8-33U/L)*; total protein 8.1 g/dL (*6-8.0g/dL*)
- CBC within normal limits
- Buccal sample: negative genetic testing for fibrillin 1 mutations.

Histopathology

Markedly thickened, haphazardly arranged collagen (positioned vertically, diagonally, and horizontally) and modestly increased fibrocytes within the deep reticular dermis, with subcutaneous extension and entrapment of adipose tissue.

Treatment

- Physical therapy
- Trialed sodium valproate, discontinued due to adverse effects including mood changes
- Trialed mycofenolate mofetil, discontinued due to GI distress

CASE 2

A 32-YEAR-OLD WOMAN WITH PROGRESSIVELY HARDENING SKIN

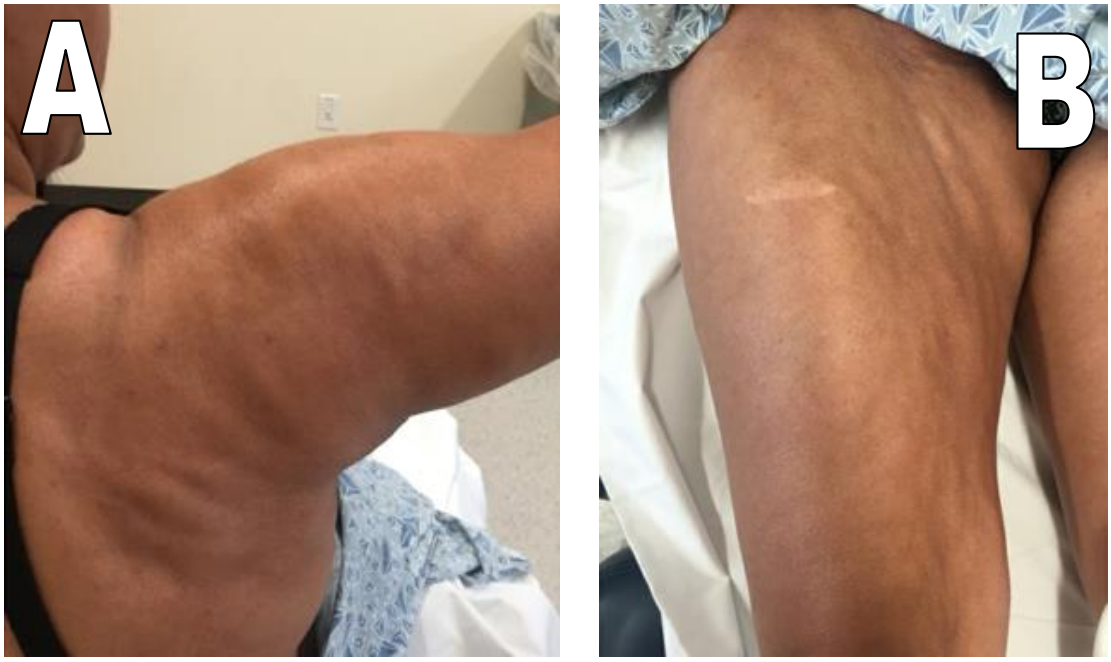

Figure 1A-B. Induration with rippling and pseudocellulite on the right thigh; subtle hypertrichosis and induration with rippling on the right arm.

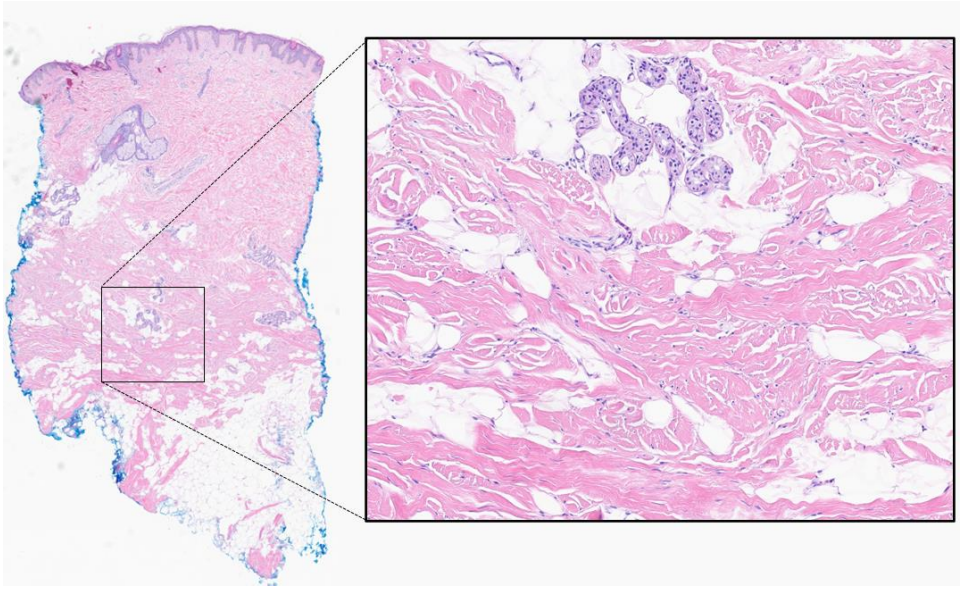

Figure 2. The examined sections show haphazard, thickened collagen with increased fibrocytes, most prominent in the deep dermis and subcutis. There is some adipose entrapment. Inflammation was absent, and features of morphea were not observed. These features are consistent with the clinical impression of stiff skin syndrome.

STIFF SKIN SYNDROME

Discussion

- Stiff skin syndrome (SSS), also known as congenital fascial dystrophy, is a rare genetic condition that presents at birth or in early childhood. It is characterized by thick, stone-hard skin, limited joint mobility secondary to induration, and mild hypertrichosis. The disease is typically non- or slowly progressive. Prognosis is generally good, but severe cases may be associated with growth retardation and restrictive pulmonary disease.
    - Lacks visceral involvement, musculoskeletal involvement, and immunologic abnormalities.
    - Most commonly affects areas with abundant fascia, frequently the thighs and buttocks.
    - A rare segmental variant has also been reported, which is asymmetrically distributed, often has later age of onset and is clinically less severe.
- Etiology of SSS is unknown; familial cases have been reported.
    - Congenital SSS is caused by an autosomal dominant mutation of the *FBN1* gene, which encodes fibrillin-1. The mutation occurs in the domain that mediates integrin binding resulting in dysregulated TGF-β signaling.
- Several histopathologic findings have been described in the literature, but most consistent findings include:
    - Increased dermal mucopolysaccharide deposition demonstrated with Alcian blue staining at pH 2.5.
    - Fascial thickening with "amianthoid-like" fibrils and bundles composed of inadequately aggregated collagen microfibrils.
- There is no definitive treatment, but management should include physical therapy.
    - Case reports have described management with oral, topical, and intralesional steroids, all with mild and incomplete effect.
    - Other treatment options described in case reports include losartan and mycofenolate mofetil, thought to reduce fibrosis via downregulation of TGF-β signaling. Methotrexate has been tried yet has shown very little efficacy.
- Differential diagnoses:
    - Scleroderma-like diseases including sclerodermatomyositis, systemic sclerosis, or localized scleroderma, nephrogenic systemic fibrosis, eosinophilic fasciitis, scleredema, scleromyxedema.

Teaching Points

- Stiff skin syndrome is a rare, non- or slowly progressive, non-immunologic condition, characterized by thick, stone-hard skin, limited joint mobility secondary to cutaneous stiffness, and mild hypertrichosis.
- Congenital stiff skin syndrome is associated with an autosomal dominant mutations of the *FBN1* gene, resulting in dysregulated TGF-β signaling.
- Medical management options are limited, but treatments targeting TGF-β signalling are possible options (e.g. mycophenolate mofetil) in a few reports. Physical therapy is essential to increase joint mobility and quality of life.

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CASE 3

A 7-YEAR-OLD GIRL WITH CUTANEOUS AND OCULAR PHOTOSENSITIVITY

Patient

LB is a 7-year-old girl.

Presenters

Kyla Pagani, MS III
Katherine Su, MD
Mehdi Rashighi, MD
Karen Wiss, MD

History

An otherwise healthy girl presented for evaluation of cutaneous and ocular photosensitivity. Since infancy, she has developed acute-onset burning pain, redness, and swelling of the skin following exposure to both ultraviolet (UV) and visible light. The episodes are associated with fatigue and typically resolve within 24 hours. At age 6 months, she developed blisters following sun exposure. She has never had any changes in urine color.

Medical History: Her prenatal course was complicated by intrauterine growth restriction. She was born at 39 weeks via normal vaginal delivery and had mild neonatal jaundice.

Family History: There is a family history of albinism in multiple maternal family members.

Allergies: None

Medications: None

Physical Examination

She is a well-appearing fair-skinned girl with blonde hair and eyelashes.

Her skin has been clear with no active rashes during each dermatology evaluation. There is no scarring or thickening on sun-exposed sites, such as the face or dorsal hands, and the nails appear normal.

Laboratory Data

- Erythrocyte protoporphyrin 236µg/dL (9/2018); 107µg/dL (11/2018) (*0-35µg/dL*)
- Zinc protoporphyrin 156µg/dL (*<100µg/dL*)
- Total porphyrins 0.3µg/L (*1.0-5.6µg/dL*)
- CBC significant for Hb 10.3g/dL (*12.1-15.1g/dL*)
- Iron 15µg/dL (*28-170*µg/dL); iron saturation 3% (*20-50%*); TIBC 583µg/dL (*255-450µg/dL*); transferrin 466mg/dL (*202-336mg/dL*); ferritin 4ng/dL (*11-306ng/dL*)
- Bilirubin 0.2mg/dL (*0.3-1.2mg/dL*); other LFTs WNL
- Vitamin D WNL
- Genetic testing not covered by insurance and therefore not performed

Imaging

- Abdominal ultrasound: increased hepatic parenchymal echogenicity (1/2019) → resolved (11/2019) and stable (6/2021)

Treatment

- Aggressive UV and visible light avoidance (her school adjusts the lighting and keeps the blinds closed)
- Sun protective clothing and broad-spectrum physical sunscreens when light avoidance is not possible
- Beta-carotene 60-90mg daily

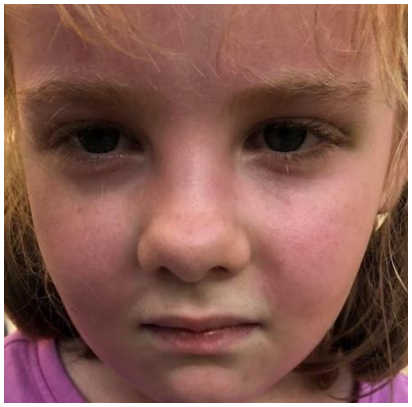

Figure 1. Skin is clear with no blisters, scarring, or thickening.

CASE 3

A 7-YEAR-OLD GIRL WITH CUTANEOUS AND OCULAR PHOTOSENSITIVITY

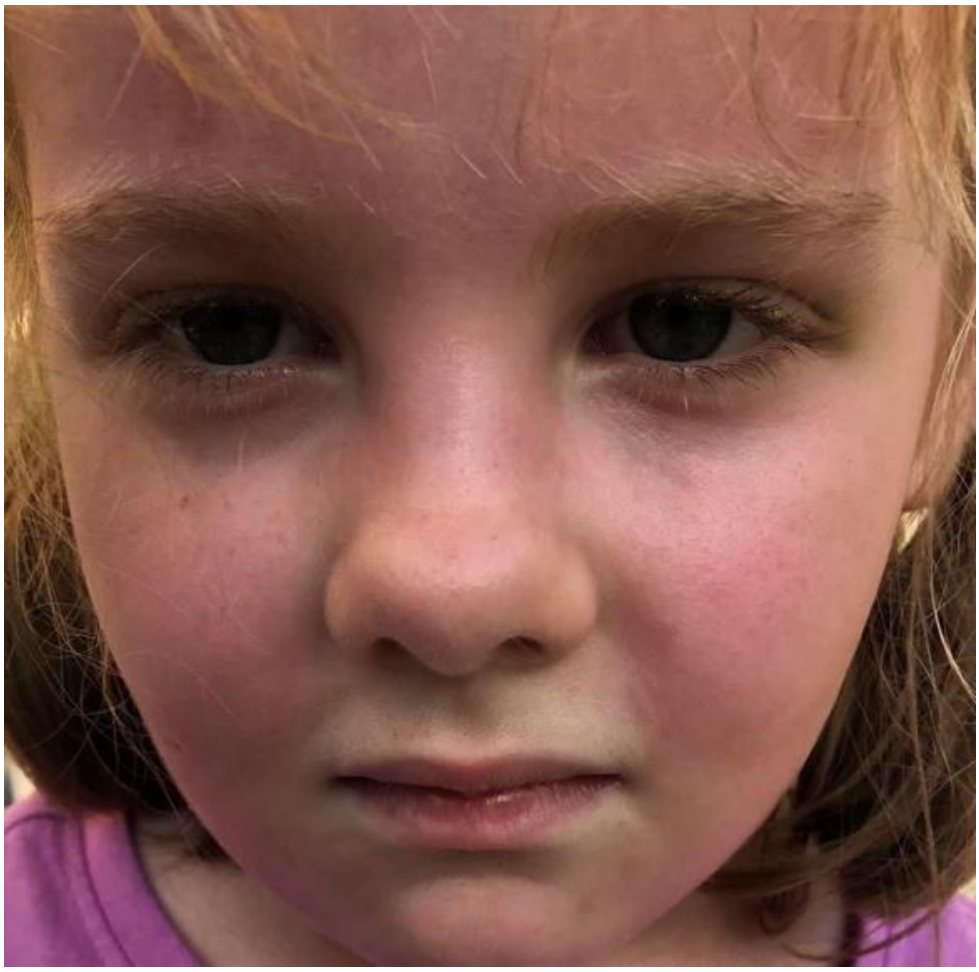

Figure 2. Skin is clear with no blisters, scarring, or thickening.

ERYTHROPOIETIC PROTOPORPHYRIA

Discussion

- Erythropoietic protoporphyria (EPP) typically presents with photosensitivity in early childhood. Patients experience acute-onset skin pain in a photo-distribution following exposure to UV or visible light. Prolonged exposure may lead to the development of erythema, edema, and, rarely, blistering or crusting of the skin. Repeated light exposure over time may lead to skin thickening, wax-like scarring, petechiae, ecchymoses, loss of lunulae of the fingernails, and vertical grooving of the lips.
- Congenital EPP is caused by autosomal recessive mutations in the the *FECH* gene, which encodes ferrochelatase, the final enzyme in the heme synthesis pathway. Late-onset EPP due to an acquired mutation has been described in the setting of myelodysplastic and myeloproliferative syndromes. Mutations in *FECH* result in accumulation of protoporphyrin IX in red blood cells. Protoporphyrins absorb light radiation (320-595nm), increasing its energy content and transferring energy to oxygen, resulting in reactive oxygen species that damage cellular proteins, lipids, and DNA.
- In EPP, erythrocyte, plasma, and stool protoporphyrins are typically elevated. An increase in zinc protoporphyrins is typical of EPP although iron deficiency and lead toxicity can also raise these levels. Urinary porphyrins are normal since protoporphyrins are not excreted in the urine. Genetic testing may aid in diagnosis.
- Patients with EPP may develop iron deficiency anemia (common) or severe liver failure (less than 5% of cases). LFTs, CBC, and vitamin-D levels should be monitored. Ultrasound of the abdomen should be performed if there is concern for cholelithiasis.
- There is no definitive treatment for EPP, but sun protection and avoidance of UV and visible light is crucial.
    - Afamelanotide, a synthetic alpha-melanocyte-stimulating hormone that increases skin pigmentation and decreases cytokine and free radical production, is available as an implant and may help to decrease pain and improve quality of life. Unfortunately, pediatric dose implants are not available.
    - Beta-carotene may help increase sunlight tolerance.
    - Calcium and vitamin D supplementation is often necessary due to sunlight avoidance.
    - Pain management may include cool compresses, non-steroidal anti-inflammatory drugs (NSAIDs), or, in severe cases, opioids.

Teaching Points

- Congenital EPP is caused by an autosomal recessive mutation in the *FECH* gene, which results in accumulation of RBC protoporphyrins.
- EPP is characterized by acute, painful, non-blistering photosensitivity, and patients are prone to anemia and liver disease.
- Delays in diagnosis are common. Patients (especially children) often have normal skin exams. Clinicians must carefully listen to the history and consider EPP in any patient with acute, non-blistering photosensitivity.
- Patients should avoid sunlight and fluorescent lighting.
- Afamelanotide and beta-carotene may be considered along with calcium and vitamin-D supplementation.
- Long-term GI follow-up is needed due to the risk of cholelithiasis and liver failure.

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1.Lecha M, Puy H, Deybach JC. Erythropoietic protoporphyria. *Orphanet J Rare Dis*. 2009;4:19.
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CASE 4

A 19-YEAR-OLD ADOLESCENT MAN WITH WOOLLY HAIR AND PALMOPLANTAR KERATODERMA

Patient

CH is a 19-year-old Caucasian adolescent man.

Presenters

Jack Hanna, MSI
Holly Neale, MSIV
Vijaya Daniel, MD, MPH
Karen Wiss, MD

History

A 19-year-old man with a *desmoplakin* (DSP) gene mutation and heart failure presented to dermatology for severe calluses on the palms and soles that were present since infancy. The thickened skin on his palmar feet was associated with itch, cracking, and pain with walking. The calluses on his hands were associated with intermittent pain. He has tried apple cider vinegar soaks, scraping, and over-the-counter creams with little improvement. The hair on his scalp has been tightly curled since birth and is styled in waves given how unruly it is to manage. He has 7 teeth that never grew back after losing his primary teeth.

Past Medical History: Arrhythmogenic right ventricular dysplasia with chronic combined systolic and diastolic heart failure and severe dilated cardiomyopathy, status-post implantable cardioverter defibrillator

Family History: Father with heart failure, woolly hair, keratoderma, and DSP mutation; paternal half-brother with woolly hair and palmoplantar calluses

Allergies: None

Medications: Amiodarone 200 mg daily, carvedilol 6.25 mg BID, Entrestro 24-26 mg BID

Physical Examination

On the first, second, and third left palmar fingers, there are yellow hyperkeratotic papules and plaques in a linear configuration. Bilateral plantar soles have thick, hyperkeratotic plaques and fissuring, primarily along pressure points, heels, and interdigital spaces. All ten toenails are thick and rugose with brown/yellow discoloration. The mouth reveals bilateral spaces between the lower teeth near the first and second premolars. The scalp hair is tightly curled and coarse and styled in waves. There are follicular-based pink papules on the lateral upper arms, lower abdomen, and the back.

Laboratory Data

- *Desmoplakin* (DSP) gene mutation, exon 14, c.1790C>T (p.Ser597Leu), heterozygous

Treatment

- Urea 40% cream daily to palms/soles
- Cerave SA daily to lateral upper arms

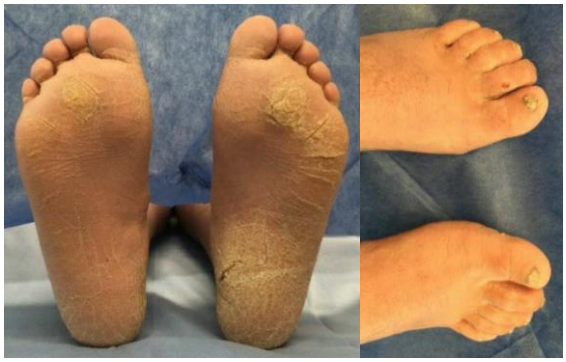

Fig 1. On plantar surfaces, thick yellow hyperkeratotic plaques with fissuring, primarily on pressure points and ten of ten yellow/brown, thick, rugose toenails.

CASE 4

A 19-YEAR-OLD ADOLESCENT MAN WITH WOOLLY HAIR AND PALMOPLANTAR KERATODERMA

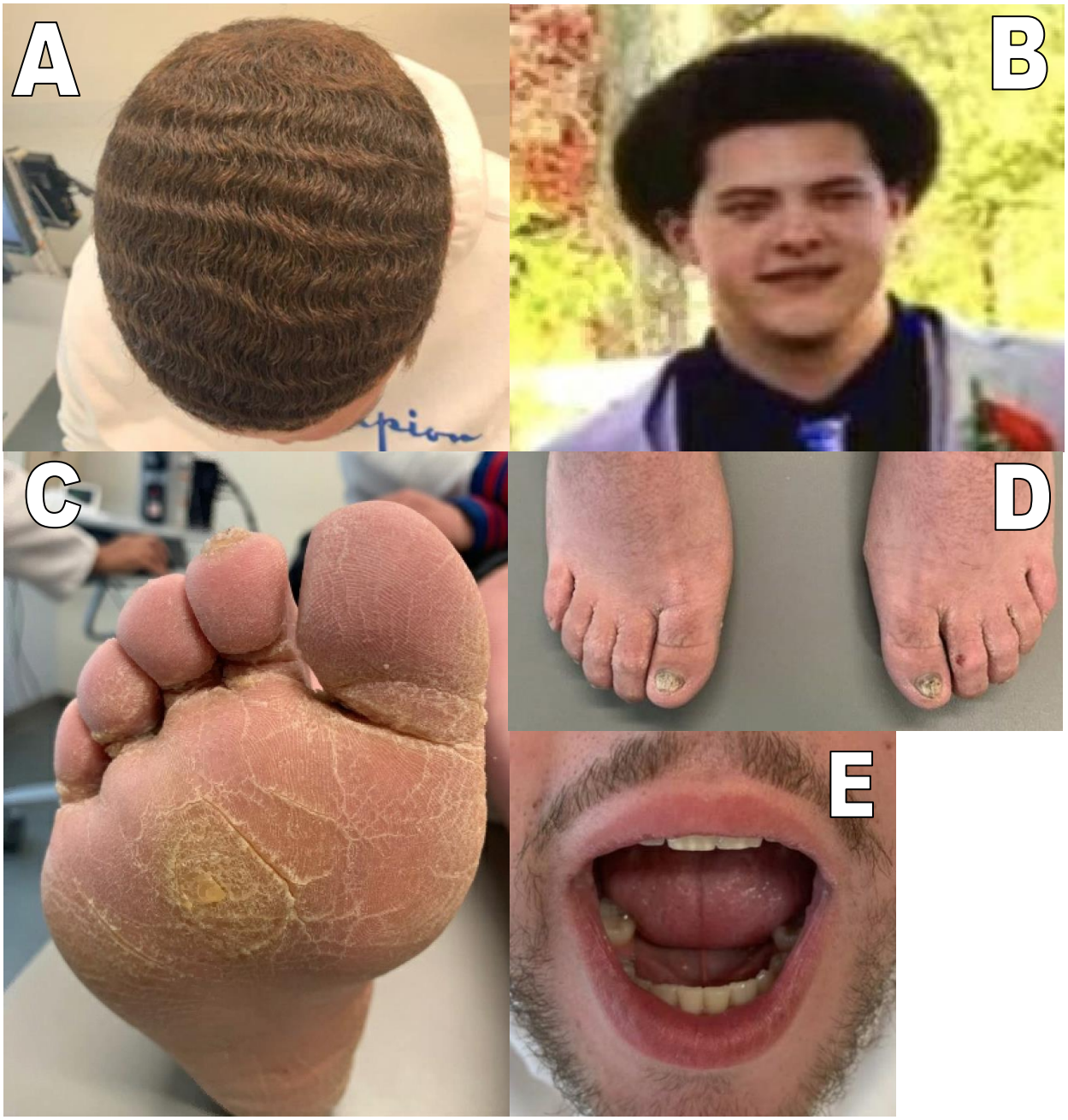

Figure 2 A-E. Scalp hair is coarse, tightly curled and styled in waves; patient's submitted photo of scalp hair that is coarse, curly hair; thick, hyperkeratotic plaque on plantar surface with thick rugose toenails; absence of right lower premolar tooth.

DILATED CARDIOMYOPATHY WITH WOOLLY HAIR, PALMOPLANTAR KERATODERMA, AND TOOTH AGENESIS (DCWHKTA)

Discussion

- Dilated cardiomyopathy with woolly hair, palmoplantar keratoderma, and tooth agenesis (DCWHKTA) is a rare autosomal dominant cardiocutaneous syndrome characterized by tightly coiled "woolly" scalp hair at birth with tooth agenesis and development of thick, linear-configured palmoplantar hyperkeratotic papules. This combination of symptoms may indicate risk of asymptomatic arrhythmogenic cardiomyopathy, which can lead to sudden death.
- In addition to palmoplantar keratoderma, cutaneous manifestations may include nail changes and keratosis pilaris.
- DCWHKTA is caused by loss of function *desmoplakin* (DSP) gene mutations affecting all three desmoplakin isoforms (I, Ia, and II) which are involved in intracellular tight junctions and epithelial cells.
- Management for DCWHKTA:
    - Cardiac management included implantable cardioverter defibrillator placement and anti-congestive heart failure treatment with beta-blockers and diuretics.
    - Dermatologic management includes soaks, emollients, paring, topical keratolytics, topical retinoids, and systemic retinoids.
- DCWHKA is distinct from autosomal recessive cardiocutaneous syndromes including Naxos Disease (type I keratoderma) and Carvajal Disease (type II keratoderma), which present with a classical phenotypic triad of woolly hair, palmoplantar keratoderma in infancy, and later development of cardiomyopathy. Naxos and Carvajal disease are differentiated by the form of cardiomyopathy (arrhythmogenic right ventricular versus dilated left ventricular, respectively).
    - Type IV keratoderma similarly involves characteristic palmoplantar keratoderma with sparse "woolly" hair and structural abnormalities to fingernails and toenails but does not result in cardiomyopathy.

Teaching Points

- Cardiac abnormalities in patients with palmoplantar keratotic elements and "woolly" hair often begin at a young age, may be asymptomatic initially and diagnosed only after nail and palmoplantar abnormalities are noticed.
- The combination of "woolly" hair and palmoplantar keratoderma, with or without teeth and nail anomalies, should prompt early cardiology and genetics referrals for diagnostic work-up and early life-saving cardiac interventions.
- Patients with DCWHKTA should be made aware of the autosomal dominant inheritance pattern for appropriate screening of family members and 50% chance to have affected offspring.

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CASE 5

A 5-YEAR-OLD GIRL WITH CAPILLARY MALFORMATIONS, LEG LENGTH DISCREPANCY, AND EPHB4 MUTATION

Patient

EP is a 5-year-old girl.

Presenters

Holly Neale, MSIV
Apoorva Trivedi, MD
Karen Wiss, MD

History

A 5-year-old girl with birthmarks and leg size discrepancy presented at age 4 years for management. Shortly after birth, her parents noticed that her left leg appeared larger and longer compared to the right, eventually impeding ambulation. An early x-ray was normal and gait improved with age. Four red-brown spots appeared on the lower chin and neck and a large brown patch appeared on her left leg and thigh in early infancy. All birthmarks have grown proportionally with the patient and are asymptomatic. An outside renal ultrasound was normal and genetic testing revealed an *EPHB4* gene mutation.

No neurologic, cardiac, or developmental issues.

Past Medical History: Otherwise healthy

Family History: Noncontributory

Allergies: None

Medications: Multivitamin

Physical Examination

On the lower chin extending to the neck are several red-brown, well-demarcated patches with no surrounding halo. On the left lateral leg extending to the thigh, buttock, and flank, is a large, confluent, irregularly bordered, light brown-pink smooth patch that is warm to touch. The left leg measures 2 cm longer than the right, with left lower extremity circumferential hemihypertrophy. Bedside handheld Doppler of the left posterior leg is positive for bruit.

Laboratory Data

- Heterozygous splicing pathogenic variant in intron 7 of the *EPHB4* gene (C.1423-6G>A)

Imaging Data

- Ultrasound of the left lower extremity reveals an asymmetrically larger left common femoral arterial diameter and pulsatile venous flow over the cutaneous patch
- An electrocardiogram and echocardiogram were both normal

Treatment

- For leg length discrepancy, pediatric orthopedics recommended shoe lifts if ambulation pain and/or tiptoeing develops
- To assess for AVMs and AVFs, future MRI/MRAs of the CNS and left lower extremity were recommended, though the patient's family has refused so far

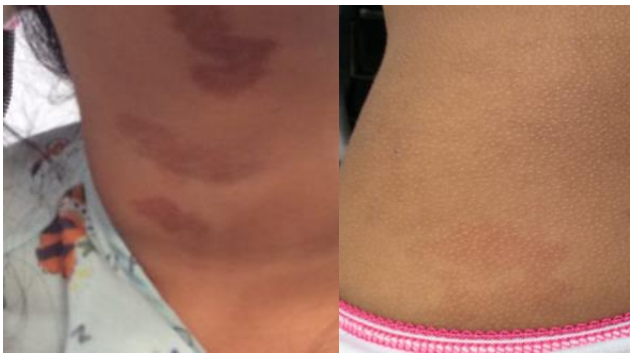

Fig 1. Red-brown capillary Malformations visible on the anterior neck and the left flank.

CASE 5

A 5-YEAR-OLD GIRL WITH CAPILLARY MALFORMATIONS, LEG LENGTH DISCREPANCY, AND EPHB4 MUTATION

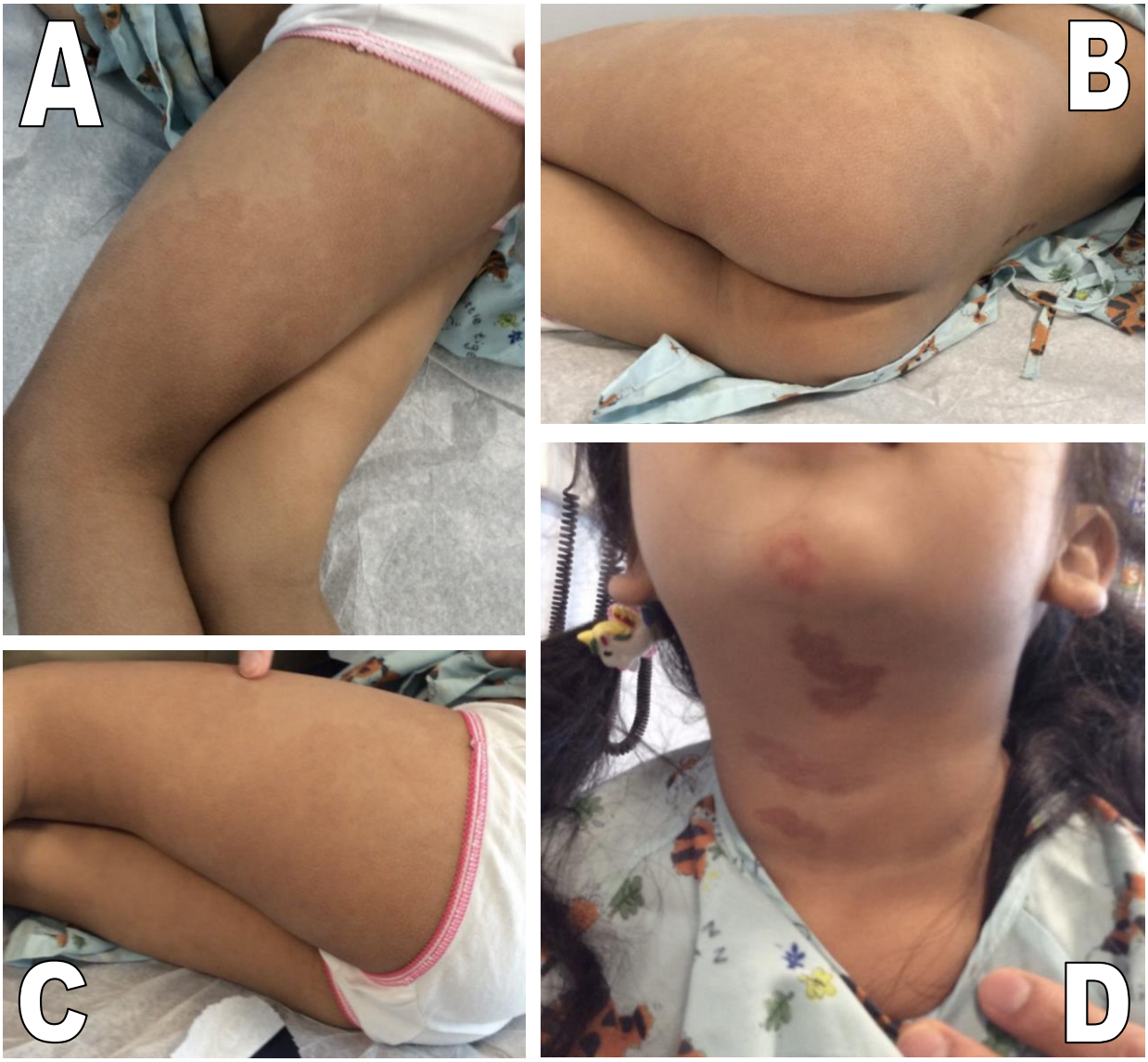

Figure 2 A-D. Red-brown capillary Malformations visible on the left leg, thigh, buttocks, and anterior neck.

CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION 2 SYNDROME WITH PARKES WEBER VARIANT DUE TO EPHB4 MUTATION

Discussion

- Capillary malformation-arteriovenous malformation syndrome (CM-AVM) is a rare autosomal dominant condition that includes multiple capillary malformations (CMs), commonly of the face and extremities. About one-third of cases have arteriovenous malformations (AVMs) and/or fistulas (AVFs) of soft tissues, bone, and the central nervous system.
- CMs typically appear early in life as pink/brown round vascular patches or macules and may have a surrounding halo. Positive clinic Doppler may suggest an arterial component.
- Parkes Weber syndrome is a phenotype affecting 8% of CM-AVM patients involving a cutaneous capillary discoloration of a limb with underlying micro-AVFs, leading to limb hypertrophy.
- Diagnosis of CM-AVM is achieved by molecular genetic testing revealing a heterozygous variant in *RASA1* (~50%) (CM-AVM1), *EPHB4* (~10%) (CM-AVM2), or unknown (~40%).
    - *EPHB4* patients may develop epistaxis and/or telangiectasias which clinically overlaps with hereditary hemorrhagic telangiectasia (HHT), a genetically distinct condition.
- Serious and/or life-threatening sequelae of associated AVMs and AVFs such as bleeding, cardiac overload/congestive heart failure, and neurologic deficits may occur.
    - Patients with CM-AVM syndrome should be screened with brain and spine MRI/MRA.
    - Cardiology referral is recommended to assess for signs of overload.
- Treatment is based on the signs present:
    - Laser is an option for CMs, though less effective if an underlying AVM is present.
    - AVM/AVF treatment depends on presentation; options include surgery or embolization.
    - If there is limb length or size discrepancy, a referral to an orthopedist is recommended.

Teaching Points

- CM-AVM2 syndrome is a rare genetic condition presenting early in life caused by mutations in *EPHB4* with some overlapping features of HHT including epistaxis and telangiectasias.
- Lesions of CM-AVM have a unique appearance between a capillary malformation and a café-au-lait macule often with surrounding pale halo.
- The Parkes-Weber variant requires monitoring for problems associated with limb hypertrophy.
- Associated AVMs and AVFs can have life threatening cardiac, neurologic, or bleeding complications that must be screened and monitored for.

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CASE 6

A 30-YEAR-OLD MAN WITH MULTIPLE SKIN CANCERS AND A WIDESPREAD ERUPTION

Patient

YS is a 30-year-old Honduran man.

Presenters

Stephanie Choi, MSI
Shauna Rice, MSIV
Mary Awad, MD
Riley McLean-Mandell, MD

History

A 30-year-old man with a history of multiple keratinocyte carcinomas treated with extensive surgery requiring skin grafting and with radiation presented to the clinic with pink-erythematous, crusted, and ulcerated plaques and nodules on the chest and left forehead. The patient grew up in Honduras with significant occupational pesticide and sun exposure. He reports a history of a rash all over his body since infancy that worsens in the sunlight.

Family History: Brother and sister with similar skin eruptions since infancy and multiple skin cancers of unknown type.

Allergies: None

Medications: None

Physical Examination

On the right upper chest, there is a 5cm x 1cm red erythematous plaque with a 1cm ulcerated nodule superiorly. Right and left parietal scalp with pink, ulcerated papules. On the scalp, face, neck, abdomen, extremities, and dorsal feet there are multiple scaly erythematous guttate papules and plaques. Numerous verrucous flat-topped papules are present on the hands and feet.

Histopathology

Shave biopsy of the lesion on the right upper chest revealed invasive SCC, moderate to poorly differentiated and extending to the tissue edges and base. Shave biopsies of two lesions on the scalp revealed nodular BCC. Punch biopsy of a guttate papule on the left shoulder demonstrated a blue-grey cytoplasmic viral cytopathic effect in squamous cells.

Treatment

- Mohs micrographic surgery with clear margins for BCC on the scalp. After four Mohs layers for the SCC on the chest, SCC in situ was appreciated at the periphery of the 7.5cm x 4cm defect. The patient elected for application of 5-fluorouracil to heal the scar for at least 4 weeks BID.
- Continues regular follow-up for CSE and excision of recurrent keratinocyte carcinomas.

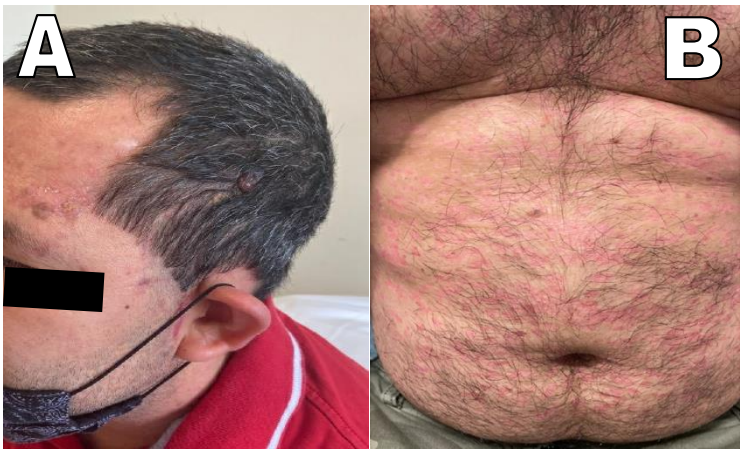

Figure 1: A. Left forehead with pink erythematous ulcerated plaque. B. Abdomen with pink erythematous well circumscribed flat-topped papules. Of note, this photo was taken at follow-up visit.

CASE 6

A 30-YEAR-OLD MAN WITH MULTIPLE SKIN CANCERS AND A WIDESPREAD ERUPTION

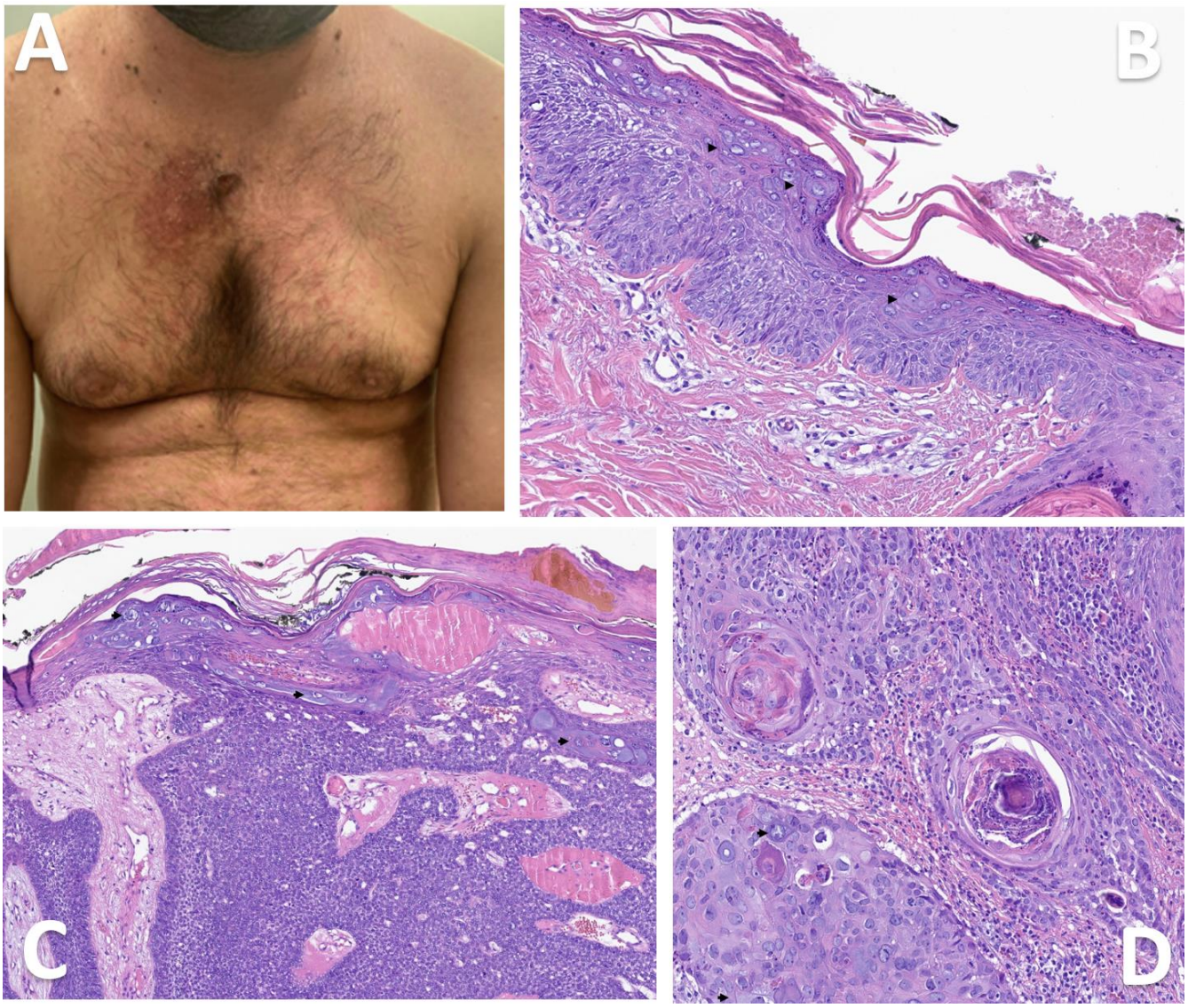

Figure 2: A. Red erythematous plaque with an ulcerated nodule superiorly on right upper chest. **B-D.** Multiple biopsies were performed, including a punch biopsy of the shoulder that demonstrated a blue-grey cytoplasmic viral cytopathic effect in squamous cells (arrowhead), consistent with epidermodysplasia verruciformis. Similar viral cytopathic changes are also seen in the scalp and chest biopsies, overlying BCC and SCC, respectively (arrows showing EDV changes in a BCC and invasive SCC).

EPIDERMODYSPLASIA VERRUCIFORMIS

Discussion

- Epidermodysplasia verruciformis (EV) is a rare skin disorder with an unusual susceptibility to infections by human papillomavirus (HPV), mainly β-HPV, followed by α-HPV. The incidence of EV is unknown, but a 2017 review literature identified ~500 reported cases of EV worldwide.
- EV is characterized by widespread eruptions of tinea versicolor-like macules and verruca plana-like lesions, and an increased risk of keratinocyte carcinomas on sun-exposed areas, notably squamous cell carcinoma (SCC). HPV-5 and HPV-9 are associated with about 90% of the EV-related SCC.
- EV can be divided into genetic EV and acquired EV. Genetic EV can be further divided into classic EV or non-classic EV. Genetic EV typically has an early onset and shows complete penetrance during infancy or early childhood. The underlying mechanism of the disease is unclear, but a defect in keratinocyte-intrinsic immunity to HPV is suspected.
- Classic EV, which accounts for ~75% of all EV cases, is a Mendelian condition inherited in an autosomal recessive manner. It is associated with loss-of-function mutations of the EVER1/TMC6 and EVER2/TMC8 genes, which are involved in cell-mediated immunity against HPV. About 30-70% of classic EV patients eventually develop keratinocyte carcinomas.
- Non-classic EV refers to EV with genetic mutations other than those in the EVER genes. It is genetically heterogenous and involves a wide variety of inheritance patterns.
- Treatment options include surgical removal of malignant lesions and nonsurgical treatments (eg, systemic retinoids, topical imiquimod) for symptomatic improvement. In classic EV, acitretin administration was reported to be efficacious in treating warts. Interferon alpha-2a can also be used in combination with acitretin.

Teaching Points

- Based on the early onset of symptoms and family history of EV-like features, this patient likely has a form of genetic EV. Genetic testing is needed to confirm the classification and subtype.
- Differential diagnosis could include warts, hypogammaglobulinemia, infections and myelokathexis syndrome (WHIM syndrome), severe combined immunodeficiency, or generalized verrucosis (GV), which is a progressive and chronic form of cutaneous HPV infection. Though GV was described as synonymous with EV in the past, they are now considered separate entities, distinguishable by their histopathology and genotypes of HPV involved.
- EV-associated cutaneous carcinomas are predominantly associated with HPV-5 infection, which is suspected to have a carcinogenic role. Because EV cutaneous carcinomas mostly arise on sun-exposed areas, it has been suggested that HPV-5 plays a co-carcinogenic role with ultraviolet radiation, though this theory is debated. Further research is needed to better understand the pathological role of HPV in carcinogenesis.

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CASE 7

A 7-month-old boy with a congenital depigmented patch on the right side of face

Patient

EF is a 7-month-old Hispanic boy.

Presenters

Alec Gramann, MSIV
Ryan Chen, MSI
Vijaya Daniel, MD, MPH
Karen Wiss, MD
John Harris, MD, PhD

History

A healthy infant presented with acongenital white patch on the right side of his face that do not cross the midline. The patches have not changed in appearance and are asymptomatic. Initial physical, neurology, and ophthalmology evaluations were unremarkable.

Past Medical History: None

Family History: His maternal grandfather and maternal 3rd cousin have a history of albinism. Patient's sibling has no pigmentary abnormalities.

Pregnancy and Birth History: Normal spontaneous vaginal delivery at 40 weeks with no complications

Medications: None

Physical Examination

Segmental depigmented patches that do not cross the midline on the right forehead, right cheek, and right nose. Poliosis at superior aspect (white forelock) overlying depigmented patch on right forehead. Poliosis of right eyebrow and eyelashes of right eye with well demarcated, but feathery edges. No heterochromia irides or lateral displacement of inner canthi. Hypopigmented area highlighted with Wood Lamp, but did not appear "porcelain-white".

Laboratory Data

- A shave biopsy was performed within the depigmented patch with feathery borders on the right cheek due to suspicion of mosaic depigmentation from a segmental distribution of albinism. A saliva sample was also collected for genetic analysis as a control specimen. Both samples were sent to Yale University/Dr. Keith Choate for mosaicism analyses.

Histopathology

Results pending

Treatment

- Strict sun protection with high SPF (SPF 100+) as well as hats. Practice sun avoidance if possible.

Figure 1. Photos from 7 months of age. Hypopigmented patches on right forehead with poliosis of right eyelashes and eyebrow shown on left. White forelock shown at right.

CASE 7

A 7-month-old boy with a congenital depigmented patch on the right side of face

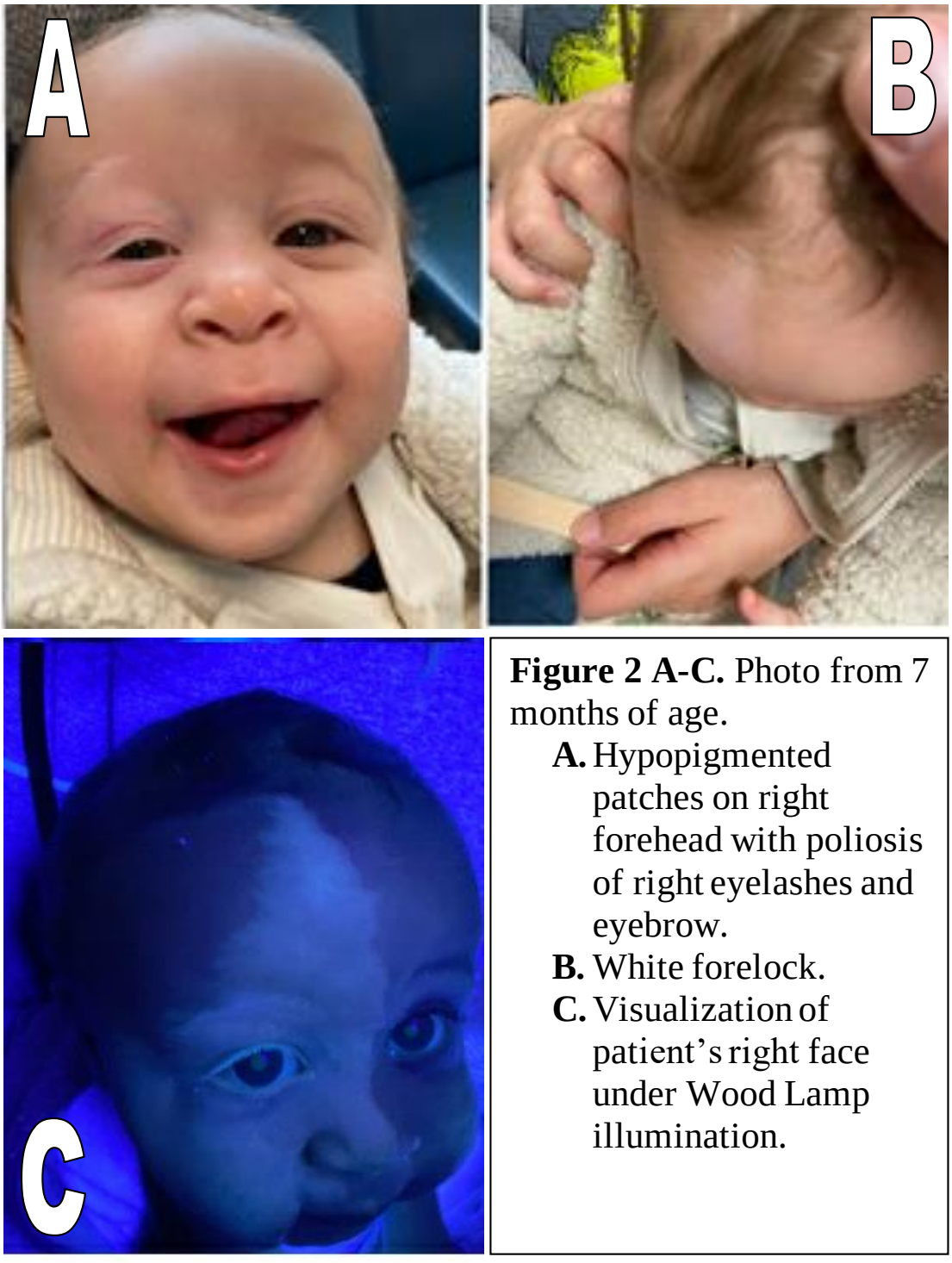

Figure 2 A-C. Photo from 7 months of age.

- **A.** Hypopigmented patches on right forehead with poliosis of right eyelashes and eyebrow.
- **B.** White forelock.
- **C.** Visualization of patient's right face under Wood Lamp illumination.

EVALUATION FOR 'SEGMENTAL ALBINISM'

Discussion

- Oculocutaneous albinism involves the disruption of melanin production by melanocytes through mutations in many genes involved in melanin synthesis, including *TYR*, *OCA2*, *TYRP1*, and *SLC45A2*. This can result in complete depigmentation or hypopigmentation based on remaining melanin synthesis pathway function. The prevalence of albinism worldwide is estimated to be approximately 1:17,000. In most cases, it is inherited in an autosomal recessive fashion and is often apparent shortly after birth.
- The segmental distribution present in this patient suggests that a somatic/post-zygotic mutation, representing a loss of heterozygosity, in a gene involved in pigment production is responsible for the absence of pigment in only a subset of melanocytes. We suggest this presentation represents "segmental albinism".
- Similar unilateral and segmental presentations of depigmentation can occur in segmental vitiligo, although it is most often acquired, rather than congenital. In addition, piebaldism is autosomal dominant, and is often associated with symmetrical white patches, as well as a white forelock of hair. Nevus depigmentosus can show segmental white patches on the face; however, true depigmentation is uncommon in nevus depigmentosus, which generally presents with hypopigmentation due to either decreased melanin production, decreased melanocyte density, or both. The fluorescence under Wood's lamp and complete absence of melanin histologically suggest an alternative diagnosis.
- Developmental conditions associated with oculocutaneous albinism include deafness, decreased visual acuity, strabismus.
- Differential diagnosis include the following:
    - Vitiligo (segmental), piebaldism, pigmentary mosaicism, nevus depigmentosus, oculocutaneous albinism (subtypes 1-7), Chediak-Higashi syndrome, Hermansky-Pudlak syndrome, Menkes disease, Waardenburg syndrome, Tietz syndrome, Griscelli syndrome, Hypomelanosis of Ito, Alezzandrini syndrome

Teaching Points

- Congenital segmental patches of depigmentation may not represent congenital segmental vitiligo, but rather a loss of heterozygosity for albinism, which we suggest represents "segmental albinism".
- Biopsy and timing of presentation may help to determine the underlying cause of depigmentation and furthermore distinguish absence of functioning melanocytes that is often acquired (vitiligo) versus congenital reduction or absence of melanin (albinism).
- In patients with cutaneous albinism, additional follow up to monitor auditory and visual function is necessary. While segmental albinism has not previously been described, to our knowledge, this diagnosis seems likely for this patient.

References:

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CASE 8

A 17-YEAR-OLD FEMALE WITH NYSTAGMUS, HYPOPIGMENTED SKIN, YELLOW HAIR AND GRAY IRISES

Patient

CZ is a 17-year-old African female.

Presenters

Kelly Barry, MSIV
Isabella Plumptre, MBBS
Leah Belazarian, MD

History

A 17-year-old female presented for evaluation of light skin and hair. Originally from the Republic of the Congo, she endured persistent and severe discrimination that forced her family to emigrate to Uganda (when she was 13), then to Kenya, and finally to the United States under refugee status 3 months prior to her visit. She reported a history of white skin and hair since birth and progressive visual impairment. Over time, her hair became more yellow in appearance. She has a history of several severe sunburns but has no personal history of skin cancer.

In detailing her experience growing up in Africa, she shared that her mother was instructed by relatives to kill her "yellow" daughter at birth, and her father was encouraged to leave his wife because of the "yellow baby", thought to indicate evil. Additionally, as the blood of people with albinism is thought to help win elections, she was forced to remain out of sight of government officials and stay home from school when political officials were visiting her village. She hopes to return to Africa in the future to educate others about people with albinism.

Past Medical History: Acne, hirsutism

Family History: Two of nine siblings with albinism. One older sister with sickle cell anemia. Parents are deceased (victims of a massacre in the Republic of Congo).

Medications: Cholecalciferol

Physical Examination

Bilateral nystagmus at baseline. Grey irises. Light skin. Red/bronze dyed hair with some undyed yellow hair present over left temporal scalp. Copper to light-brown hair in the groin and axilla. Dark brown reticular, ink spot-like macules and patches on the posterior neck, right forearm, face, and ears. Brown terminal hairs along the chin and jawline bilaterally.

Laboratory Data

- Genetic testing: compound heterozygote with two pathogenic variants of OCA2 NM_000275.2 (a) deletion of exon 7 and b) c.1094del p.Ala365Glufs*5)

Treatment

- OCA2: Sun protection counseling, frequent complete skin exams, ophthalmology and genetics consult

CASE 8

A 17-YEAR-OLD FEMALE WITH NYSTAGMUS, HYPOPIGMENTED SKIN, YELLOW HAIR AND GRAY IRISES

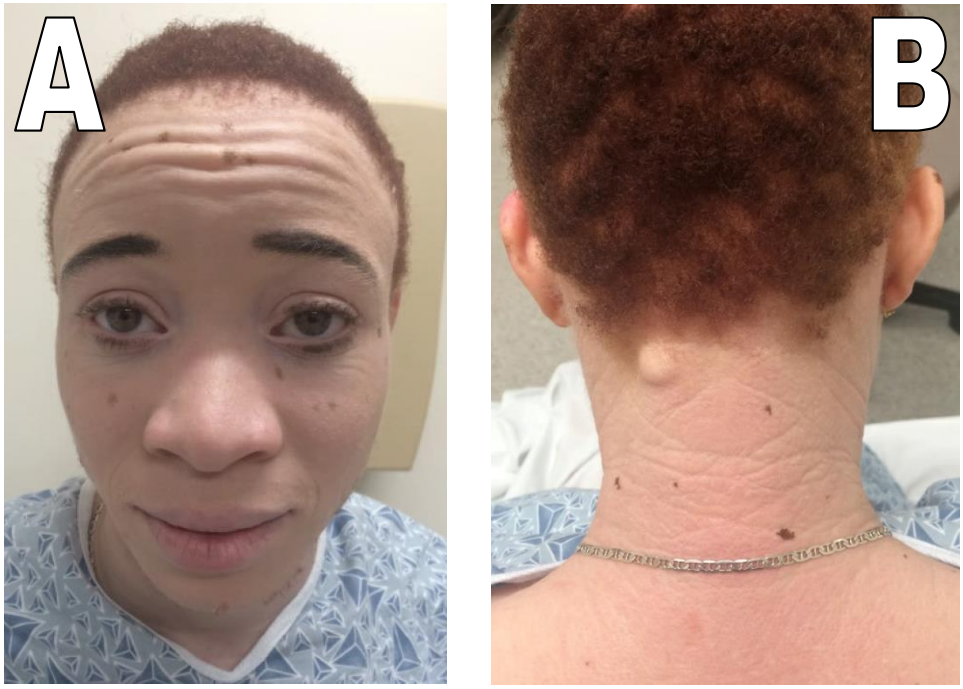

Figure 1 A+B: Light skinned female with red hair (dyed), gray irises, and few dark brown reticular macules across forehead, cheeks, and posterior neck. (Epidermal inclusion cyst left occiput).

OCULOCUTANEOUS ALBINISM TYPE 2

Discussion

Epidemiology, Clinical & Genetic Characteristics:

- Oculocutaneous albinism (OCA) is a heterogeneous group of disorders of melanin biosynthesis characterized by reduced or absent pigmentation of the hair, skin and eyes.
- Clinical characteristics, genotype, and mode of inheritance of the more common OCA subtypes are outlined in **Table 1.** There are eight known subtypes (OCA1-7) caused by mutations in genes encoding either enzymes or membrane transporter proteins involved in melanin synthesis or tyrosine accumulation. The prevalence of OCA2 can be as high as 1:3,900 in African populations.
- Most people with OCA2 are compound heterozygotes, harboring two different mutations in one gene. Molecular characterization can be helpful for diagnosis, management, and genetic counseling.

Psychosocial Impact:

- The persecution and stigmatization of people living with albinism (PWA) in some regions of Africa have garnered international attention where infanticide, kidnapping, amputations, and decapitations have been committed in the name of witchcraft, superstition, and wealth.
- Some cultures have stigmatizing names for PWA, such as “nguruwe” which means pig or “zeru” which means ghost. Children are isolated from peers, who may refuse to eat or play with them, and family who may perceive them as evil. Family members are also frequently subjected to stigmatization and harassment, resulting in severe psychosocial distress.
- In some regions, it is cultural practice to place children with albinism in the sun to “accustom their skin” to UVR, which, coupled with lack of access to healthcare, manifests as higher and earlier incidence of skin cancer and mortality. In sub-Saharan Africa, PWA are at a 1000-fold greater risk for developing squamous cell carcinoma (SCC) compared to the general population, and often present with advanced neoplasms due to delayed diagnosis and treatment.
- Increased awareness of albinism, promotion of social and societal integration, improved access to healthcare, and discouragement of consanguineous marriages could help mitigate misconceptions, reduce prevalence, and minimize preventable morbidity.

Teaching Points

- OCA2 has a higher prevalence in African populations and is caused by autosomal recessive mutations in *OCA2.*
- The psychosocial impact of albinism is substantial in regions of the world where myths and superstitions can lead to stigmatization, discrimination and persecution.
- PWA in sub-Saharan Africa often may not have access to adequate sun protection, and are at greater risk of SCC.

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OCULOCUTANEOUS ALBINISM TYPE 2

Clinical & Molecular Characteristics of Oculocutaneous Albinism Subtypes[1]				
Subtype	**Prevalence**	**Inheritance Pattern, Gene**	**Dermatologic characteristics**	**Associated Findings**
OCA1 OCA1A	1:40,000*	AR, *TYR* Absent	White hair/eyelashes/eyebrows, white skin (does not tan)	Pink to light blue & fully translucent iris, significantly reduced visual acuity (1/10 or less), nystagmus, intense photophobia
OCA1B ("yellow albinism")		Decreased	Hair/skin may develop pigment over time (1 to 3 years) varying from white to blond or light brown. OCA1B-TS variant has temperature sensitive tyrosinase activity, leading to white hair at central sites, and pigmented hair at acral sites	Blue to green/brown iris, significantly reduced visual acuity
OCA2 ("red OCA")	1:36,000 (white Europeans); 1:3,900-1:10,000 (Africans)	AR, *OCA2* (P gene)	Varied skin pigment (generally more than OCA1), hair may develop pigment over time, nevi and ephelides are common	Iris color varies (generally not pink, can be gray in Africans), reduced visual acuity
OCA3	Rare (white Europeans, Asians); 1:8,500 (Africans)	AR, *TYRPI*	Red hair and reddish-bronze skin ("Rufous") in Africans	Blue-brown iris Less prominent visual anomalies
OCA4	Rare (white Europeans); 1:85,000 (Japanese)	AR, SLC45A2	Varied skin and hair pigmentation, similar to OCA-2 (requires genetic testing to distinguish).	

CASE 9

A 28-YEAR-OLD MAN WITH NEVUS DEPIGMENTOSUS

Patient

RS is a 28-year-old Indian man.

Presenters

Lucy Xu, MSIII
Renee Joyce, MSI
Elana Putterman, MD
Maggi Ahmed, MD, PhD
Bassel Mahmoud, MD, PhD

History

A 28-year-old male presented for evaluation of a white spot on the right temple, which had been present since shortly after birth. The spot had grown in size over time and was determined to be consistent with nevus depigmentosus. Past medical treatments included homeopathic medications and various creams and lotions, none of which were effective in restoring pigmentation. The patient underwent melanocyte-keratinocyte transplant procedure (MKTP) in June 2021. At 3 month follow up, physical exam showed about 80% repigmentation of the lesion.

Past Medical History: None

Family History: Hypothyroidism (mother); no family history of vitiligo

Allergies: None

Medications: None

Physical Examination

Hypopigmented patch on the right temple and cheek, extending to the right parietal scalp, measuring approximately 7 x 5 cm with ill-defined borders

Treatment

- A donor area of 7 cm^2 on the left lateral thigh was identified, and a partial-thickness skin graft was harvested.
- The harvested skin was treated with trypsin and the epidermis was isolated and broken down into small pieces, centrifuged, and resuspended in 0.5 ml of normal saline to create a melanocyte-keratinocyte suspension.
- The recipient site (35 cm^2) was abraded with 1 pass of Erbium YAG ablative laser using 37 joules/ cm^2 fluence, at 150 micrometer depth of ablation.
- The melanocyte-keratinocyte suspension was applied to all areas of the recipient site that was subsequently covered with Puracol® collagen dressing, Adaptic®, Telfa® pads, sterile gauze, and Tegaderm®.
- An additional layer of gauze and Hypafix® was applied over the site to provide pressure.

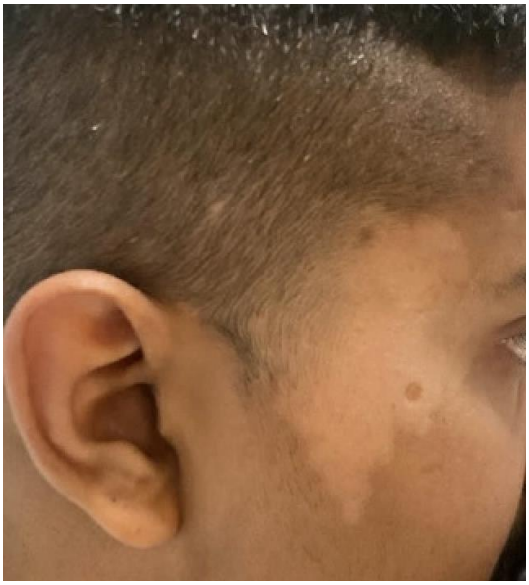

Figure 1. Nevus depigmentosus on the right temple, cheek, and parietal scalp

NEVUS DEPIGMENTOSUS TREATED WITH MKTP

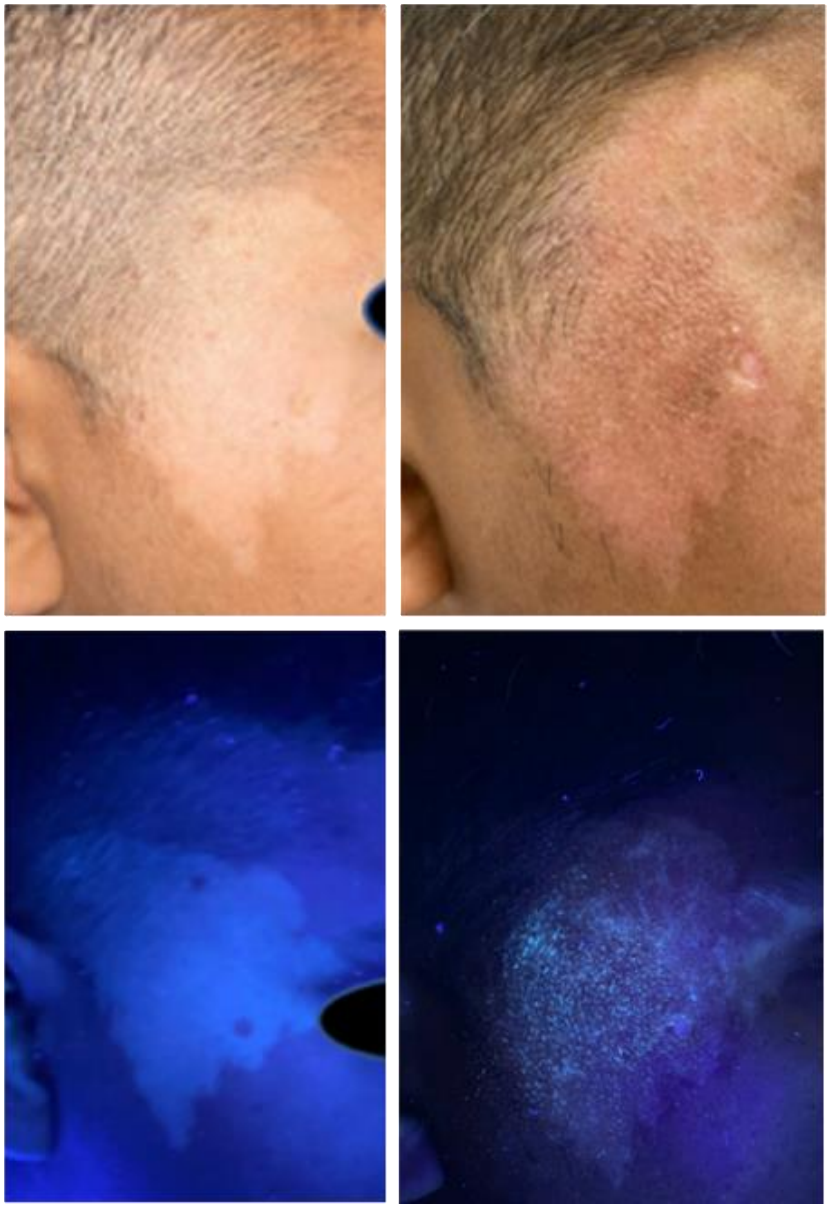

Figure 1. Before treatment with room light (top left) and with Wood lamp (bottom left). Three months after treatment with room light (top right) and with Wood lamp (bottom right).

NEVUS DEPIGMENTOSUS TREATED WITH MKTP

Discussion

- Nevus depigmentosus (ND) is a congenital nonprogressive disorder characterized by a focal hypopigmented macule or patch that remains stable over time. It generally presents during infancy or very early on in childhood (<3 years).
    - The pathogenesis of ND is not fully understood, though it is believed to be related to functional defects of melanocytes and morphologic abnormalities of melanosomes.
- Accepted diagnostic criteria for nevus depigmentosus include: (1) leukoderma present at birth or onset early in life; (2) no alteration in distribution of leukoderma throughout life; (3) no alteration in texture, or change of sensation, in the affected area; and (4) no hyperpigmented border around the achromic area.
- Several features distinguish nevus depigmentosus from vitiligo, and it is important to make the distinction in considering medical management and patient counseling.
    - In contrast to nevus depigmentosus, which is congenital, vitiligo is an acquired, autoimmune-mediated depigmentation with lesions progressing or regressing.
    - Additionally, the distribution of vitiligo is mostly symmetric and usually affects the face, genitals, hands, and feet. Under Wood lamp examination, ND lesions show an off-white accentuation without obvious fluorescence, in contrast to the chalk-white accentuation observed in vitiligo.
- Treatment is cosmetic. Approaches to repigmentation in nevus depigmentosus patients have included psoralen and ultraviolet A (PUVA), excimer laser, and surgical grafting methods, with limited degrees of success.
- Melanocyte-keratinocyte transplantation procedure (MKTP) is a surgical technique historically used to restore pigmentation in vitiligo patients who are unresponsive to medical and/or phototherapy treatments.
    - In MKTP, autologous donor cells are isolated from the epidermis of a shaved skin biopsy, resuspended, applied to the dermabraded hypopigmented site, and a collagen dressing is applied.
- Here, we report the case of a 28-year old patient who underwent MKTP for nevus depigmentosus of the right temple, which was well tolerated without complications. After three months, 80% repigmentation of the nevus was observed with additional repigmentation expected over time, highlighting the role for MKTP as an effective therapeutic approach to repigmentation in cases of nevus depigmentosus.

Teaching Points

- Nevus depigmentosus is a common congenital hypopigmented macule or patch that remains stable in shape and distribution over time, though its size typically may grow in proportion to overall body growth.
- Nevus depigmentosus can be distinguished from vitiligo by its clinical course and with Wood lamp examination, which demonstrates off-white accentuation with more poorly defined borders than vitiligo and without fluorescence.
- Melanocyte-keratinocyte transplantation may be an effective surgical treatment in restoring pigmentation in patients with nevus depigmentosus.

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CASE 10A

A 55-YEAR-OLD WOMAN WITH EPIDERMOLYSIS BULLOSA PRURIGINOSA ON THE LOWER EXTREMITIES

Patient

VN is a 55-year-old Asian-Indian woman.

Presenters

Nicole Loranger, MSIII
Zainab Abbas, MD
Leah Belazarian, MD

History

55-year-old woman presented for evaluation of a 30-year history of pruritus and blistering on the lower extremities. Her symptoms had previously been managed with oral dapsone and topical pramoxone. At the time of her presentation in January 2021, the pain and pruritus had compromised her ability to stand, work, and sleep. Prior biopsy and clinical picture was consistent with epidermolysis bullosa pruriginosa. Genetic testing has been suggested but not yet performed.

Past medical history: Hypothyroidism

Allergies: none

Family history: none

Medications:Gabapentin, levothyroxine, fluocinolone, sumatriptan, acetaminophen

Physical Examination

General: Well-appearing Asian-Indian female in no acute distress

Skin:

January 2021: Confluent hyperpigmented plaques with central erosions noted on bilateral lower legs and dorsal feet. Fingernails and toenails were dystrophic with some anonychia and dorsal pterygium.

February 2021: Persistence of hyperpigmented plaques with central erosions on bilateral lower legs and dorsal feet. Dupilumab injections were increased to weekly, and this resulted in the first noticeable improvement in pruritus for the patient.

June 2021: Significant reduction in pruritus, blistering, and crusting noted at follow up. The patient was very pleased with the progress as it had resulted in improved sleep since the last visit.

Pathology

DIF and EM biopsies were performed in November 2011. EM results were considered suggestive for dystrophic epidermolysis bullosa; DIF was inconclusive.

Treatment

- 300mg subcutaneous injection of Dupixent® (dupilumab) was prescribed in January 2021 for administration once every other week following a loading dose of 600 mg.
- Dupilumab therapy was increased to 300 mg weekly due to minimal improvement after two months of every other week injections.
- Concomitant VBeam laser therapy was performed in February, April, and June of 2021 with some added benefit.

CASE 10A

A 55-YEAR-OLD WOMAN WITH EPIDERMOLYSIS BULLOSA PRURIGINOSA ON THE LOWER EXTREMITIES

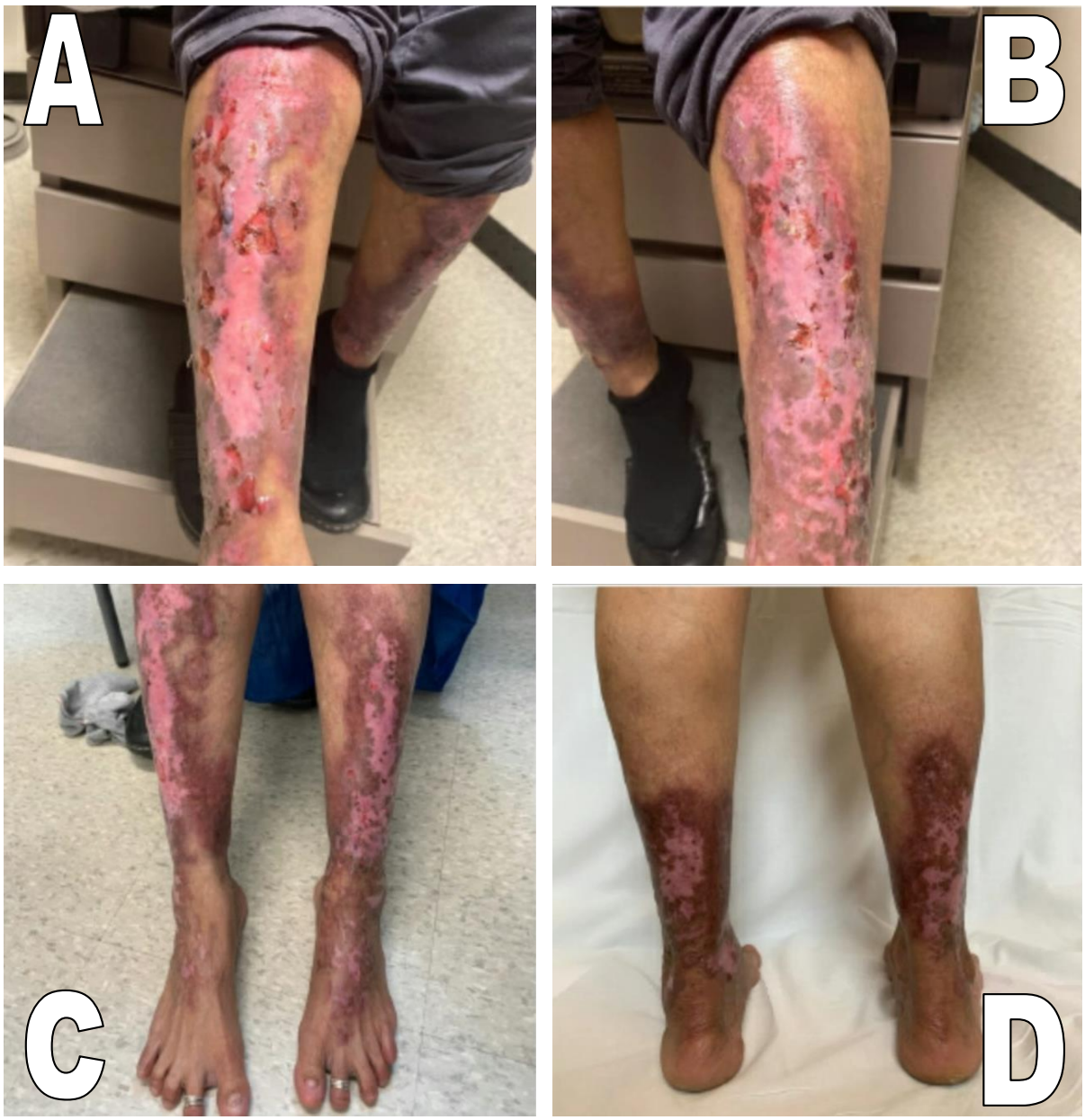


Figure 1 A-D: Extensive erosions, tense bullae, milia, and atrophic/hyperpigmented scarred plaques on the bilateral anterolateral and posterior lower legs.

CASE 10B

A 26-YEAR-OLD WOMAN WITH EPIDERMOLYSIS BULLOSA PRURIGINOSA ON THE LOWER EXTREMITIES

Patient

SC is a 26-year-old woman.

Presenters

Nicole Loranger, MSIII
Zainab Abbas, MD
Karen Wiss, MD

History

The patient was referred for evaluation of progressive worsening of pruritus and blistering on bilateral hands, feet, and upper thighs, in addition to a lifelong history of oral mucosal blistering. The localization of lesions to lower extremities and the age at onset suggested the EB pruriginosa variant of dominant dystrophic epidermolysis bullosa. Previous attempts to control pruritus by outside providers included topical steroids, oral doxycycline and niacinamide.

Past medical history: none

Allergies: none

Family History: Mother has a mild case of EB (subtype unknown)

Medications: Doxycycline, niacinamide, triamcinolone 0.1% ointment, hydroxyzine, famotidine, escitalopram

Physical Examination

General: Well-appearing female in no distress

Skin:

February 2021: Multiple tense blisters on hands, feet, and thighs. Left dystrophic great and 2nd toenails.

July 2021: Healing erosions on lower legs.

October 2021: Small blisters on tongue, few blisters and healing erosions on bilateral lower legs. Left dystrophic great toenail.

Pathology

H&E and DIF performed in Maine and at MGH in October 2020. H&E showed a subepidermal blister suggestive of bullous hypersensitivity reaction. DIF was inconclusive.

Genetic Testing

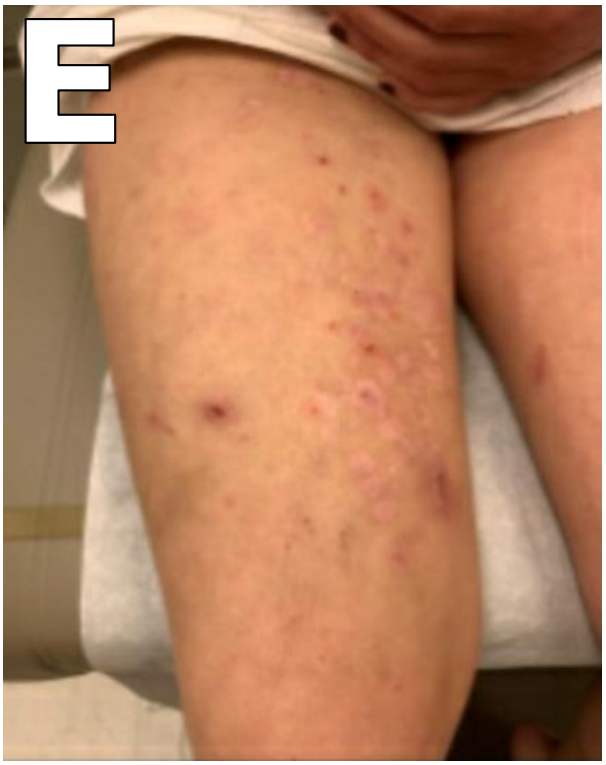
Genetic testing was performed in March 2021 and a pathologic variant c.7787del was identified in the COL7A1 gene. Mutations in this gene are associated with dominant dystrophic epidermolysis bullosa.

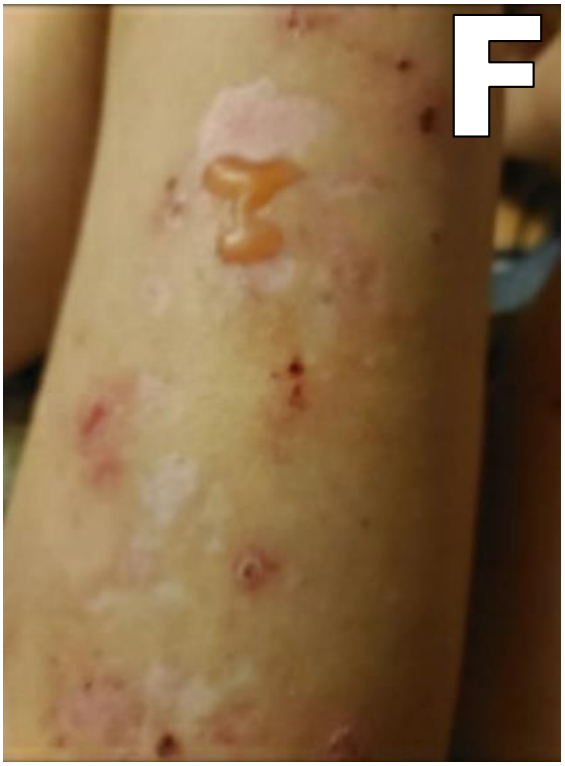
Treatment

- 300mg injection of dupilumab was prescribed in July 2021 for administration once every other week following a loading dose of 600 mg.
- Patient has had 2 rounds of dupilumab and has noted some improvement in itch.
- Continued use of triamcinolone ointment 0.1% is recommended in addition to dupilumab.

CASE 10B

A 26-YEAR-OLD WOMAN WITH EPIDERMOLYSIS BULLOSA PRURIGINOSA ON THE LOWER EXTREMITIES





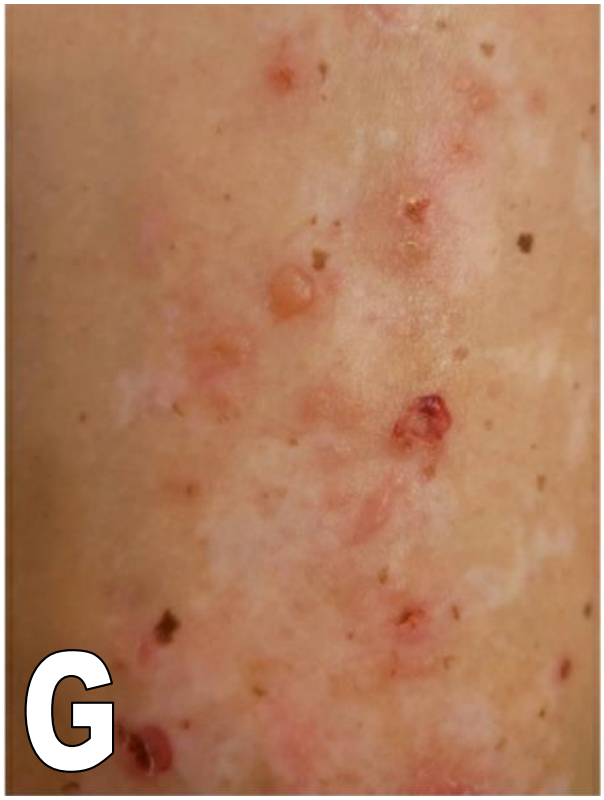
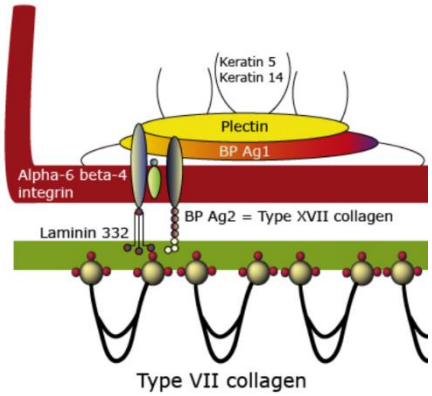


Figure 2 E-G: Multiple tense bullae and healing erosions with overlying hemorrhagic crust on the bilateral lower extremities.

EPIDERMOLYSIS BULLOSA PRURIGINOSA TREATED WITH DUPILUMAB

Discussion



- Epidermolysis bullosa pruriginosa (EBP) is a rare form of dominant or recessive dystrophic epidermolysis bullosa (DDEB or RDEB).
- DDEB is the result of a mutation in the COL7A1 gene, which encodes for the type VII collagen fibrils that anchor the epidermal basement membrane to the dermis below.
- Disruption of this connection predisposes the affected individuals to pruritus, pain, and bouts of blistering following mild trauma to the skin.
- The EBP subtype is classified clinically by the presence of lower extremity bullae, generally accompanied by intense pruritus and pain, erosions, and scarring. It is common for the severity of these symptoms to greatly impact the patients' ability to sleep, work, or perform basic activities of daily life.
- Dupixent® (dupilumab) is a monoclonal antibody that targets the IL-4Rα/IL-13 axis, which is involved in type 2 inflammation and skin barrier dysfunction; it has been previously used in the treatment of atopic dermatitis and prurigo nodularis, which share clinical similarities with EBP.

Teaching Points

- EBP can be a challenging condition to diagnose as it often mimics hypertrophic lichen planus, bullous lichen planus, and prurigo nodularis.
- Genetic testing can help significantly in diagnosing EBP, a subtype of DEB, and should be performed when possible, as ascertaining the diagnosis is important for determining the appropriate course of treatment.
- Treatment of EBP can also prove challenging given the severity of pruritus and pain, and control of these symptoms is not easily achieved through the previously available immunomodulators or other anti-pruritics.
- Dupilumab has been very effective in decreasing the intensity of pruritus and pain experienced by patients with refractory EBP, as demonstrated by these three patients as well as the cases described by Dr. Rich Antaya, et al. in the attached reference.

References:

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CASE 11

A 14-YEAR-OLD MALE WITH BULLAE AND CHRONIC NON-HEALING EROSIONS

Patient

RS is a 14-year-old Caucasian male.

Presenters

Lucy Xu, MSIII
Kelly Flanagan, MSIV
Sarah Servattalab, MD
Karen Wiss, MD

History

RS has been followed since birth for bullae at sites of friction and non-healing ulcers and was started on oral ataluren in May 2019 for junctional epidermolysis bullosa. In the months preceding initiation of treatment, the patient had multiple hospitalizations for unexplained fever, elevated inflammatory markers, and nausea. Expanded access was granted by the FDA on a compassionate basis for the use of ataluren. At his most recent follow-up, the patient had not had any hospitalizations since starting the treatment twenty-four months prior and continued to demonstrate improvement in wounds and reduction of granulation tissue.

Past Medical History: GERD, iron deficiency anemia, corneal abrasions, tracheal stenosis (status post tracheostomy), posterior reversible encephalopathy syndrome, chronic constipation, chronic hyponatremia

Allergies: Lanolin (rash), neomycin (rash), peanut (rash), sweet potato (rash)

Medications:
• betamethasone dipropionate 0.05% cream
• chlorhexidine 4% external liquid
• desonide 0.05 % ointment
• gabapentin 100-200 mg PRN
• hydrocortisone sodium succinate 75 mg SQ q8h PRN
• hydroxyzine HCL 10 mg po TID PRN
• mupirocin 2% ointment twice daily
• white petrolatum 41% topical ointment

Physical Examination

School-aged boy in a wheelchair with feeding gastrostomy tube, tracheostomy and many ulcers at various stages of healing on the trunk and extremities. Height and weight are both <1% for age.

Laboratory Data

- Complete metabolic panel without abnormalities
- CBC without leukocytosis
- Ongoing microcytic anemia with up-trending total iron binding capacity and down-trending ferritin
- Genetic testing demonstrated heterozygous mutations in LAMB3: p.R635x in exon 14 and IV58-1G→A in intron 8

Histopathology

Punch biopsies taken from normal-appearing skin at baseline failed to detect laminin-332 by direct immunofluorescence or electron microscopy. Biopsies at 10 months after treatment showed subtle staining of laminin-332 at the basement membrane zone. The patient declined an additional biopsy at 24 months. We are currently exploring other techniques to quantify the change in laminin-332.

Treatment

Ataluren TID: 250 mg morning and midday, 500 mg at night (total daily dose of 40 mg/kg).

CASE 11

A 14-YEAR-OLD MALE WITH BULLAE AND CHRONIC NON-HEALING EROSIONS

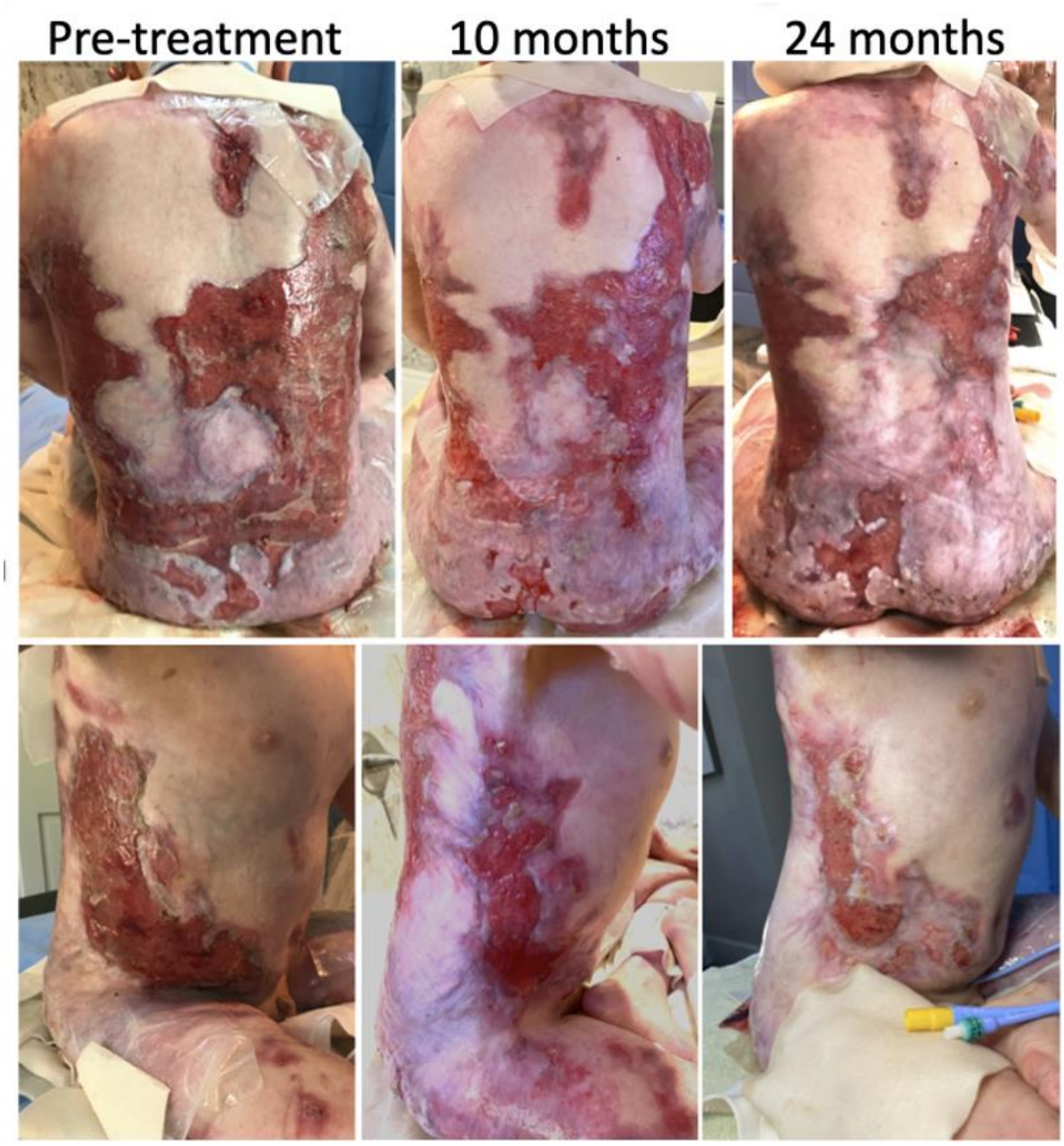

Figure 1. Ulcers at various stages of healing on the trunk, buttocks, and lower extremities. Top row: Patient's back pre-treatment, at 10 months and at 24 months. Bottom row: Patient's right flank pre-treatment, at 10 months and at 24 months of treatment.

CASE 11

A 14-YEAR-OLD MALE WITH BULLAE AND CHRONIC NON-HEALING EROSIONS

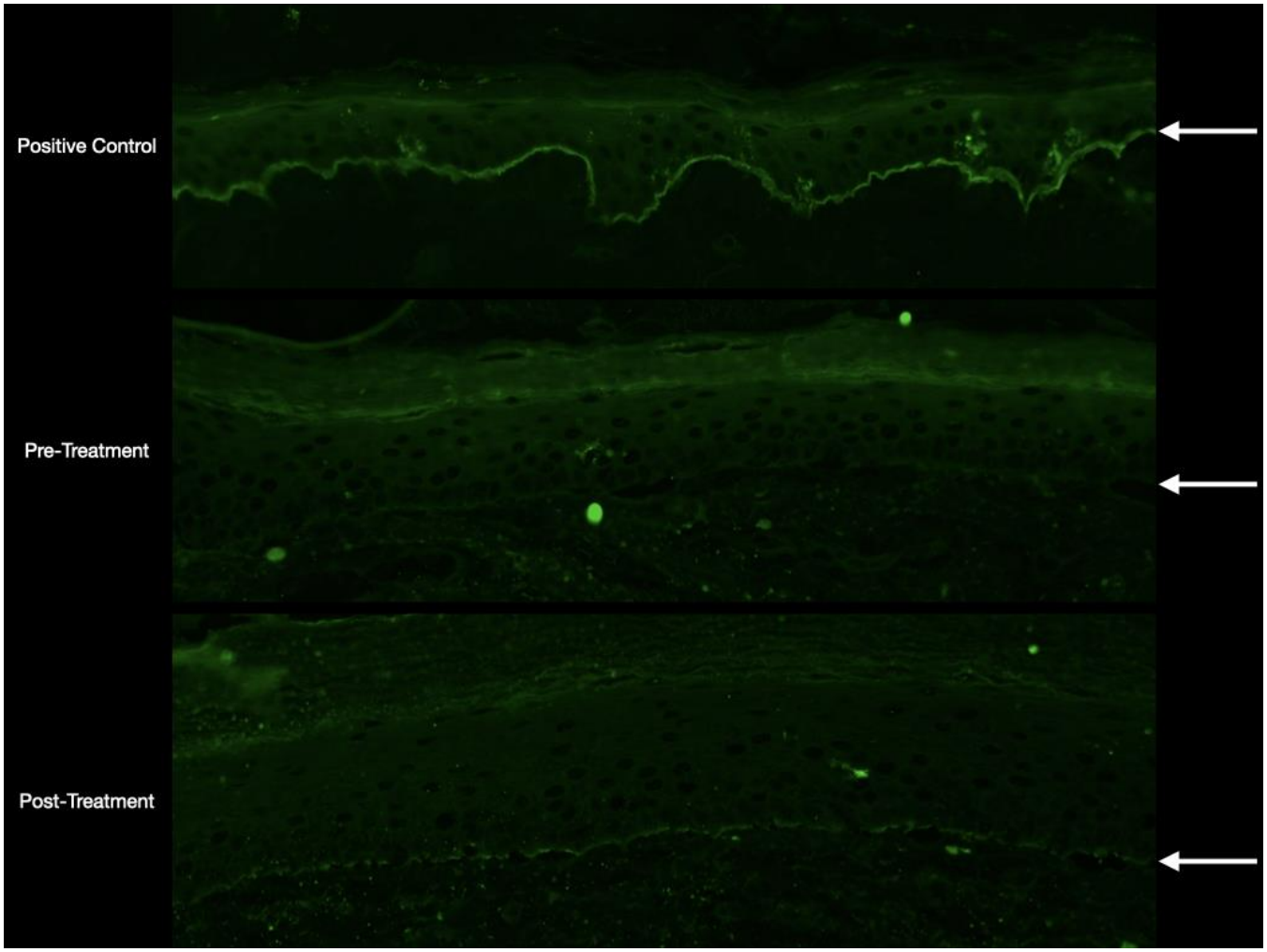

Figure 2. Direct immunofluorescence staining for laminin 332 from skin biopsy. Top row: Positive control. Middle row: No staining detected prior to starting treatment. Bottom row: Faint staining observed at the basement membrane zone 10 months after starting ataluren.

JUNCTIONAL EPIDERMOLYSIS BULLOSA, GENERALIZED INTERMEDIATE TYPE, ON ORAL ATALUREN

Discussion

- Epidermolysis bullosa (EB) is a group of inherited disorders characterized by extremely fragile skin that blisters easily with minor trauma.
    - Junctional EB (JEB) is a subtype of EB in which blisters form within the lamina lucida of the basement membrane zone. When due to defects in laminin 332, they can be further characterized as generalized severe (Herlitz) and generalized intermediate (non-Herlitz/nH).
    - Our patient has a severe form of generalized intermediate JEB that has resulted in significant laryngeal and cutaneous involvement. More severe forms, formerly termed Herlitz type, result in early death.
- JEB often involves nonsense mutations in LAMA3/LAMB3/LAMC2 (which encode different constituent polypeptide chains of laminin 332) leading to premature stop/termination codons (PTCO.
    - Patients commonly present at birth with generalized blisters and erosions at sites of trauma, especially in the diaper area, and with a hoarse voice. They develop excessive granulation tissue and typically have poor growth, laryngeal, genitourinary, and dental involvement.
- There is currently no cure for patients with nH JEB, and management generally focuses on symptomatic management and prevention of potentially serious complications of the disease.
    - Premature codon readthrough has proved a promising therapeutic option, and pilot clinical studies have shown that inducers of PTC readthrough such as gentamicin can be effective in restoring expression of laminin 332, though there is concern for toxicities associated with long-term aminoglycoside usage.
- In this case, we describe the novel use of ataluren (Translarna®) in a twelve-year-old patient with generalized intermediate nH JEB.
    - Ataluren, a drug currently used for treatment of Duchenne muscular dystrophy in Europe, is thought to suppress nonsense mutations by promoting the readthrough of premature termination codons.
    - Our patient has been tolerating the treatment well with no significant side effects and reports improved wound healing and fewer hospitalizations, highlighting the role of ataluren in the management of junctional and potentially other forms of epidermolysis bullosa.

Teaching Points

- Patients with non-Herlitz type, generalized intermediate type JEB typically have chronic wounds with excess granulation tissue that rarely heal.
- Current management approaches for EB are mostly palliative, but PTC readthrough therapies such as ataluren may be effective for promoting wound healing and preventing serious complications of JEB.

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CASE 12

A 48-YEAR-OLD WOMAN WITH DERMATOMYOSITIS PRESENTS WITH PROGRESSIVE ULCERATING PLAQUES AND DYSPNEA

Patient

MR is a 48-year-old Caucasian woman.

Presenters

Kelly Flanagan, MSIV
Apoorva Trivedi, MD
Nikki Levin, MD, PhD
Mehdi Rashighi, MD

History

A 48 yo female was admitted to the hospital for worsening rash and shortness of breath on exertion. Eight months prior, the patient developed a rash around her eyes, knuckles, palmar hands, face, and thighs. The rash was associated with fatigue, joint pains, and a 50 lb. weight loss. Initial evaluation by an outside dermatologist included a biopsy which favored dermatomyositis. Prior evaluation by rheumatology demonstrated SSA and MDA-5 antibody positivity, along with restrictive lung disease on pulmonary function tests. The patient denied significant muscle weakness. Prior to admission, she was taking prednisone, hydroxychloroquine, and mycophenolic acid. Her pulmonary symptoms progressed, requiring admission. Dermatology was consulted due to painful ulcerations, and worsening rash on the bilateral breasts, elbows, and thighs.

Past Medical History: GERD, HTN, hepatic steatosis
Medications: hydroxychloroquine, prednisone, mycophenolic acid, folic acid, pyridoxine, aspirin

Physical Examination

On the dorsal knuckles, PIP, and DIP joints were pink to violaceous smooth thin papules, some with ulceration. Pink papules were seen on ventral PIP, DIP, and palmar surfaces. Dilated capillary loops were present on the majority of proximal fingernail folds. Pink-erythematous, thin plaques were present around bilateral eyes. On chest, back, and shoulders were bright pink plaques with minimal scale. On the bilateral elbows, breasts, and inner thighs were large, thin, pink-erythematous ulcerating plaques.

Laboratory Data

- ANA negative, anti-Smith negative, RNP negative, SSA (+) 2.7, SSB negative
- Myositis Panel: positive for MDA-5 Ab, Aldolase (+) 11.2, CK not elevated, CRP wnl, ESR 24.
- PFTs: restrictive with moderately reduced DLCO
- CT Chest: bilateral peribronchial ground glass opacities

Histopathology

None

Treatment

- Continued treatments: aspirin, methylprednisolone, mycophenolic acid, and hydroxychloroquine
- Treatments started: High dose IVIG and pentoxifylline 400mg TID as tolerated, with the latter for cutaneous ulcerations

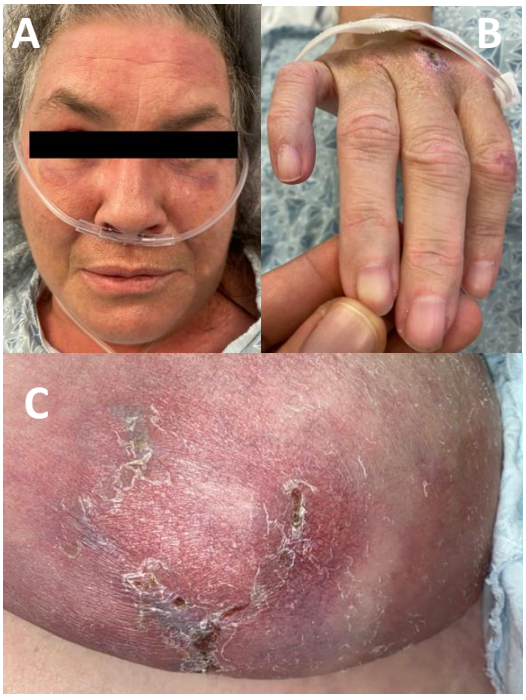

Figure 1A-C. Heliotrope rash (A), ulcerated Gottron papules (B), ulcerated breast lesions (C)

CASE 12

A 48-YEAR-OLD WOMAN WITH DERMATOMYOSITIS PRESENTS WITH PROGRESSIVE ULCERATING PLAQUES AND DYSPNEA

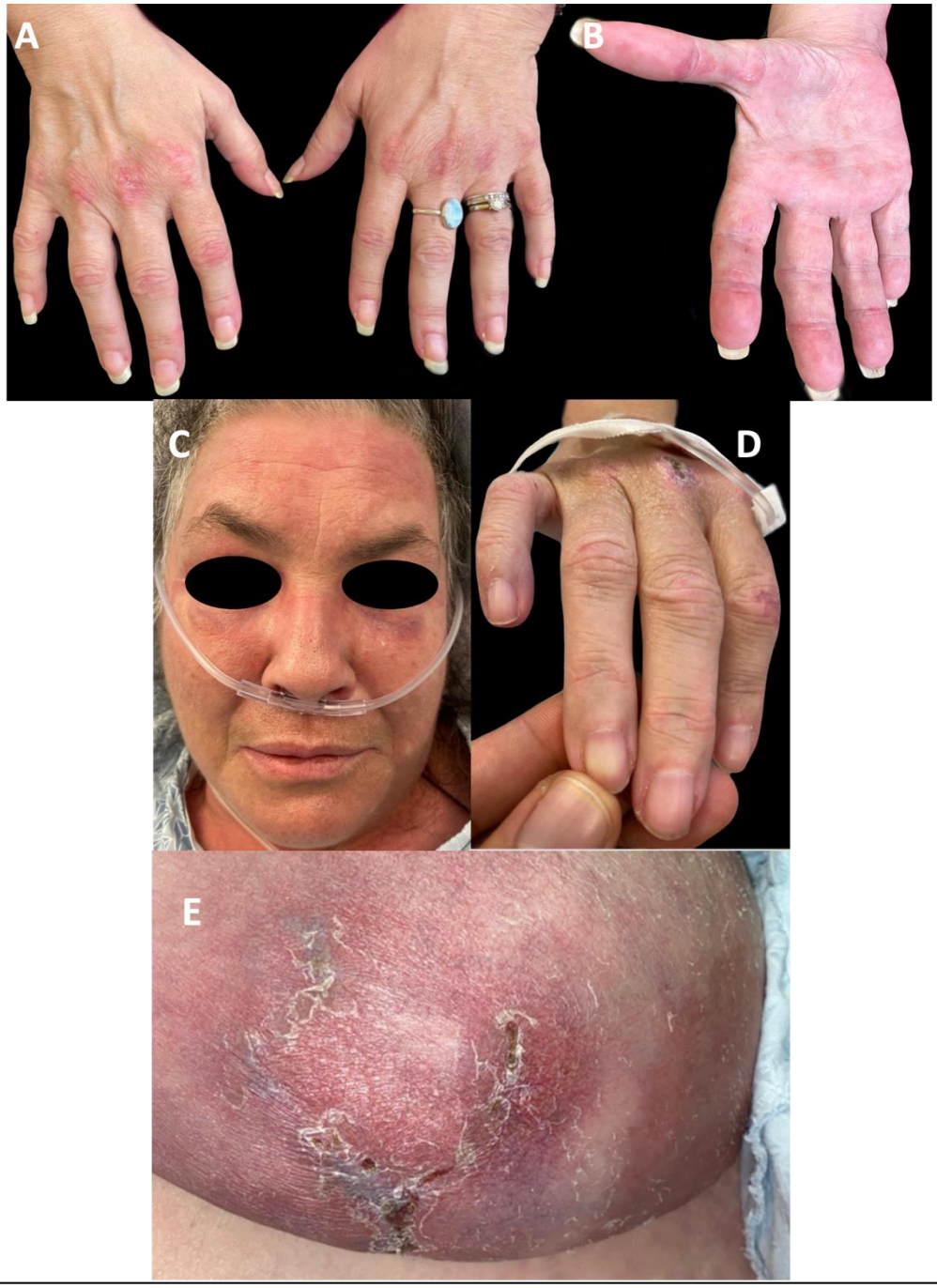

Figure 1A-E. Gottron papules (A) and inverse Gottron papules on palmar hands (B) are noted at patient's initial clinic visit prior to ILD development. Also seen are heliotrope rash (C), ulcerated Gottron papules (D), and an ulcerated plaque on breast (E) upon our evaluation.

ANTI-MDA5 POSITIVE DERMATOMYOSITIS

Discussion

- Anti-melanoma differentiation-associated gene 5–positive dermatomyositis (MDA5+ DM) is a rare, recently defined form of dermatomyositis. In addition to characteristic dermatomyositis cutaneous findings, MDA5+ DM presents with mucocutaneous ulceration, nonscarring alopecia, palmar papules (inverse Gottron papules), panniculitis, arthritis, and rapidly progressive interstitial lung disease (ILD).
- Inverse Gottron papules, which our patient initially presented with before developing pulmonary symptoms, are strongly associated with ILD and anti-MDA5 antibodies.
- Three distinct patient subgroups of anti-MDA5 have been identified: anti-MDA5+ DM with rapidly progressive ILD and poor prognosis, anti-MDA5+ rheumatic DM with good prognosis, and anti-MDA5+ vasculopathic DM with intermediate prognosis. Anti-MDA5+ with RP-ILD is the most fitting for our presented patient.
- MDA5 antibodies are dermatomyositis-specific, and they are generally not found with other positive myositis specific antibodies (MSAs).
- ILD occurs in an estimated 42-100% of anti-MDA5 dermatomyositis patients. ILD is defined by ground-glass opacification and fibrosis of lung parenchyma on CT imaging. Interestingly, cutaneous ulceration is the strongest predictor of developing ILD.
- ILD in anti-MDA5 dermatomyositis can be rapidly progressive and fatal. Early detection and aggressive immunomodulatory treatment, therefore, has been shown to improve patient outcomes.
- While dermatomyositis has known association with malignancy, the anti-MDA5 subtype may have reduced risk of malignancy. Malignancy, however, has been rarely reported in the anti-MDA5 subtype.

Teaching Points

- Due to risk of rapidly progressive ILD, recognition of MDA5+ DM diagnosis and initiation of treatment is critical.
- Inverse Gottron papules should raise concern for MDA5+ DM and progression to ILD and is known as the “inverse Gottron sign.”
- ILD screening should be performed for any suspected or confirmed case of MDA5+ DM. Screening should include high resolution CT. If CT is not possible, pulmonary function tests with DLCO can be used as an initial screening test. If these are abnormal, a CT must be performed to evaluate for and characterize ILD.
- Providers should repeat PFT screening with DLCO every 3-6 months for first year after diagnosis and should routinely take a detailed history of pulmonary symptoms at each patient encounter.
- MDA5 antibody titers may be useful for monitoring disease activity and for predicting disease flare.
- All adult patients with dermatomyositis, including MDA5+ DM, should be screened for malignancy.
- Treatments for MDA5+ DM should include immunomodulator and immunosuppressive therapies depending on systemic organ involvement. For improved symptom management, vasodilators (nifedipine, sildenafil) can be used to treat underlying vasculopathy. Aspirin and pentoxifylline can also improve peripheral circulation.

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CASE 13

A 22-YEAR-OLD FEMALE WITH HISTORY OF JUVENILE DERMATOMYOSITIS MANAGED WITH MYCOPHENOLATE MOFETIL WITH NEW FIRM PINK RASH ON BOTH LEGS

Patient

RC is a 22-year-old Caucasian female.

Presenters

Emilee Herringshaw, MSIII
Heather Gochnauer, MD
Mehdi Rashighi, MD

History

A 22-year-old female with a known history of juvenile dermatomyositis treated and well controlled on mycophenolate mofetil (MMF) and hydrocortisone developed new asymptomatic firm pink to red plaques on multiple areas of both lower extremities over the course of a few months.

Past Medical History: Juvenile dermatomyositis (predominantly muscle disease, diagnosed in 2012), adrenal insufficiency secondary to chronic prednisone therapy (2018)

Family History: Rheumatoid arthritis in maternal grandmother, systemic sclerosis, and Raynaud phenomenon in paternal grandfather

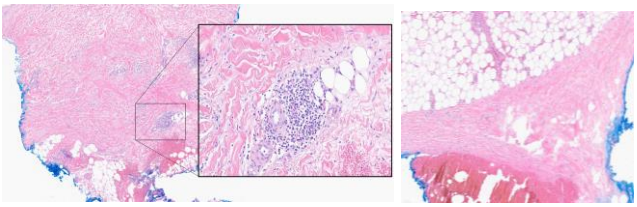
Medication Allergies and Side Effects: Vancomycin (rash), methotrexate (MTX) (fatigue and visual hallucination), IVIG (aseptic meningitis)

Medications: Vitamin D3 one daily, fludrocortisone 0.05 mg oral 3x weekly, hydrocortisone 10 mg oral AM and 5 mg PM, ethynodiol diacetate and ethinyl estradiol tablets (Kelnor) one daily, mycophenolate mofetil 500 mg oral twice daily

Physical Examination

RC is a well-appearing, white female in no distress. Skin exam of the legs is significant for multiple ill-defined firm pink to red erythematous plaques on the bilateral calves. No epidermal changes or loss of follicular ostia are noted.

Histopathology



Histologic sections show a thickening and homogenization of mid-deep reticular dermal collagen and broad bands of septal fibrosis in the subcutaneous tissue. There is perivascular lymphoplasmacytic inflammation and some diminishment of fat around the deeper eccrine coil. Some of the deeper septae show sparse lymphoplasmacytic inflammation. The features are consistent with morphea profunda.

Treatment

- Topical treatment with calcipotriene 0.005% ointment twice daily on weekdays alternating with clobetasol 0.05% ointment twice daily on weekends
- Previously unable to tolerate MTX or IVIG for treatment of JDM
- Already on hydrocortisone for chronic adrenal insufficiency
- Increasing dose of MMF to 1000 mg twice daily resulted in new supraventricular tachycardia; continued MMF 500 mg twice daily
- Started on a trial of abatacept (Orencia) infusion 500 mg once monthly, which was eventually switched to 125 mg subcutaneous weekly
- After starting abatacept, existing plaques became significantly lighter, and affected areas became soft with almost complete normalization of skin texture and firmness.

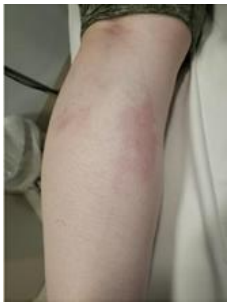


Figure 1. Left calf in February 2020 prior to treatment with abatacept.

JUVENILE DERMATOMYOSITIS WITH NEW ONSET MORPHEA PROFUNDA TREATED WITH ABATACEPT

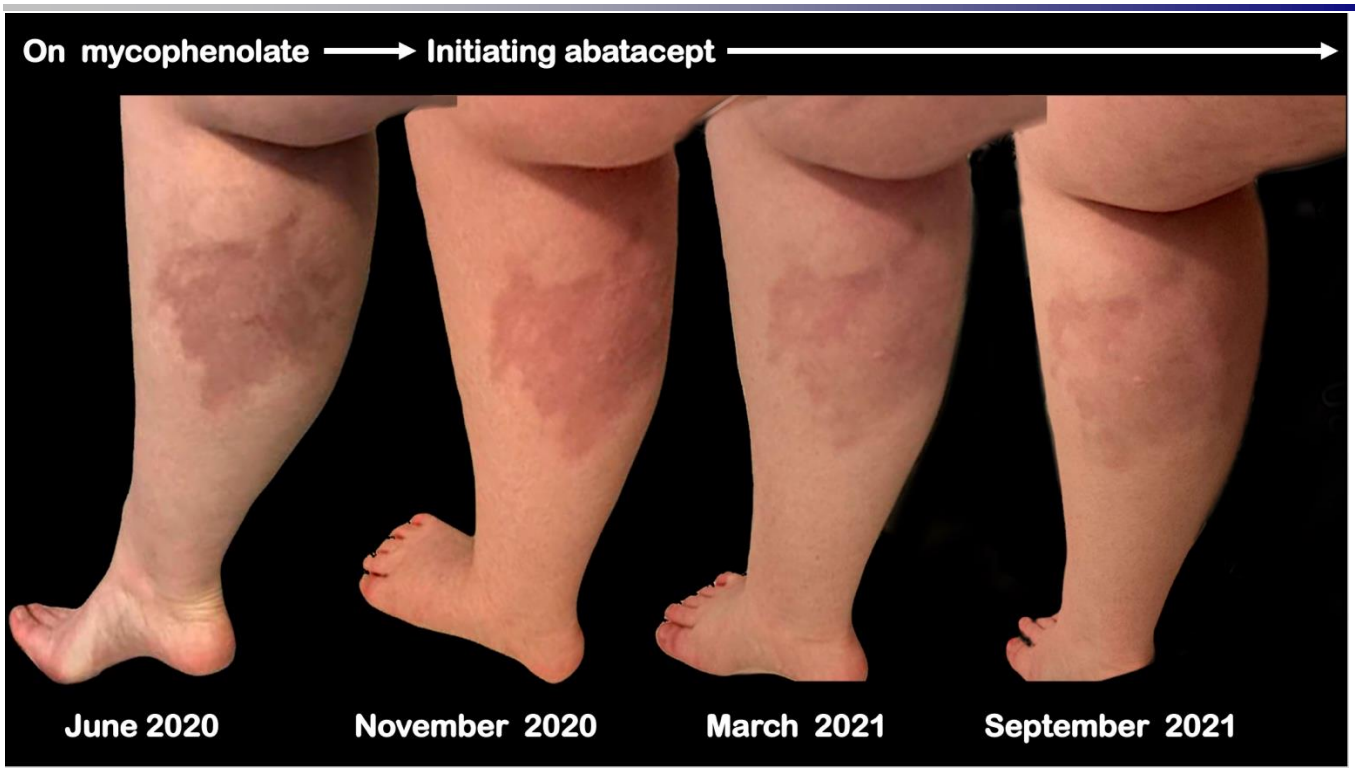


Figure 2. Right calf involvement during treatment with mycophenolate (June 2020) and abatacept (November 2020 through September 2021).

JUVENILE DERMATOMYOSITIS WITH NEW ONSET MORPHEA PROFUNDA TREATED WITH ABATACEPT

Discussion

- Morphea (localized scleroderma) is an idiopathic inflammatory skin disease with varying clinical manifestations. It can affect both children and adults. Women are more commonly affected at a rate of 5:1.
- Morphea initially presents with ill-defined patches of erythema with no surface changes, which can be associated with pain or pruritus. Untreated morphea can progress to permanent skin fibrosis and disfiguring dyspigmentation. While most cases of morphea (circumscribed or plaque) are limited to the skin, certain subsets, including linear and deep morphea, can lead to functional impairment if involving the face or overlying joints.
- Treatment of morphea is dependent on the patient's age, clinical subset, anatomical distribution, disease extent and activity. Early aggressive treatment is imperative to reduce comorbidities associated with disfiguring skin discoloration, permanent fibrosis, functional impairment, and possible damage to other organs. Current therapies include topical treatments with corticosteroids, calcineurin inhibitors, and synthetic vitamin D analogs. Phototherapy with ultraviolet (UV) A1 (and for more superficial cases narrow band-UVB) has also proved successful. The most common systemic therapies used for treatment of morphea include MTX and MMF.
- Recently, abatacept has shown promising results in treatment of severe or resistant morphea. In a case study of three patients with deep tissue involvement, assessment at 6 and 18 months demonstrated tolerability and dramatic improvement, particularly with regards to reversible of fibrosis in affected areas. Assessment of patient clinical signs and symptoms, whole-body MRI, and mean Modified Rodnan Skin Score indicated improvement from baseline by 37% at 6 months and 74% by 18 months, with no significant adverse outcomes noted.
- In another multicenter cohort study performed to evaluate refractory juvenile localized scleroderma, patients were treated with abatacept and assessed for up to 24 months. The patients had initially failed MTX and/or MMF and glucocorticoids. Abatacept was added and nearly all 18 subjects improved. Of the 18 subjects, 15 (83%) were considered responsive, two (11%) were considered treatment failures, and one had an adverse event. Most affected subjects had improved musculoskeletal function. Notably, ten subjects managed to discontinue systemic glucocorticoid and six discontinued MTX and MMF without flaring.

Teaching Points

- Abatacept has recently been reported to be successful in treating multiple cases of morphea, including patients with severe morphea profunda.
- In several cases of morphea, abatacept halted the disease and reversed the skin fibrosis.
- This case demonstrates the promise of abatacept as a candidate for treating severe morphea. This patient did not develop any new or expanding lesions after starting abatacept and existing lesions improved.

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CASE 14

A 43-YEAR-OLD MAN WITH PAINFUL ERODED PAPULES AND PLAQUES IN THE BILATERAL INGUINAL FOLDS

Patient

JC is a 43-year-old Caucasian male.

Presenters

Emilee Herringshaw, MSIII
Vijaya Daniel, MD, MPH
Mark Scharf, MD

History

A 43-year-old male with biopsy-proven pulmonary langerhans cell histiocytosis (LCH) in 2014 presented to the Emergency Department with a 3-year-history of a painful rash in inguinal folds (right>left) progressively worsening over 5 months. He had presented to the ED 1 month before with similar symptoms and was discharged home. He tried treatment with clotrimazole cream and oral antibiotics, with some improvement, but continued to have significant pain with movement.

Past Medical History: Biopsy-proven pulmonary Langerhans cell histiocytosis (LCH) in 2014

Allergies: Amoxicillin (reaction: rash)

Relevant Medications: Morphine, gabapentin, oxycodone, clotrimazole cream, ciclopirox cream, fluconazole, trimethoprim-sulfamethoxazole, cefalexin, mometasone cream, alclometasone ointment

Social History: History of tobacco use, quit in 2014

Physical Examination

Patient was a well appearing male in no distress. He had a red plaque in his right inguinal fold with a large fissure and multiple red macules and papules with erosions extending to his right upper medial thigh and his right scrotum with malodorous discharge. In his left inguinal fold, he had a well demarcated light pink plaque with scattered papules with overlying erosions, and papules extending superiorly. His scalp had few scattered papules with crust. He had no lymphadenopathy.

Histopathology

Punch biopsy lesion from the right upper thigh shows an infiltrate of histiocytoid cells involving the epidermis and dermis. Cytologically, the cells have an expanded cytoplasm and reniform nuclei with punctate nucleoli. By immunohistochemistry, these cells are positive for CD1a and Langerin.

Imaging and Special Tests

- Lab workup: PET-CT, MRI brain and C spine, and bone marrow biopsy do not reveal other sites of disease, however his central diabetes insipidus was confirmed and is consistent with occult central nervous system (CNS) involvement; overall consistent with multisystemic LCH (skin, CNS, lung).

Treatment

- Chemotherapy: Completed 6 cycles of cytarabine with initial improvement of pain of bilateral groin but subsequent worsening. PET-CT scan showed modest response in skin and lung.
- Radiation: Radiation of left inguinal crease with almost complete resolution.
- Oral medications: Trimethoprim-sulfamethoxazole, fluconazole, oxycodone, morphine
- Topical treatment: Mometasone cream and ciclopirox cream

Figure 1. Right inguinal fold

CASE 14

A 43-YEAR-OLD MAN WITH PAINFUL ERODED PAPULES AND PLAQUES IN THE BILATERAL INGUINAL FOLDS

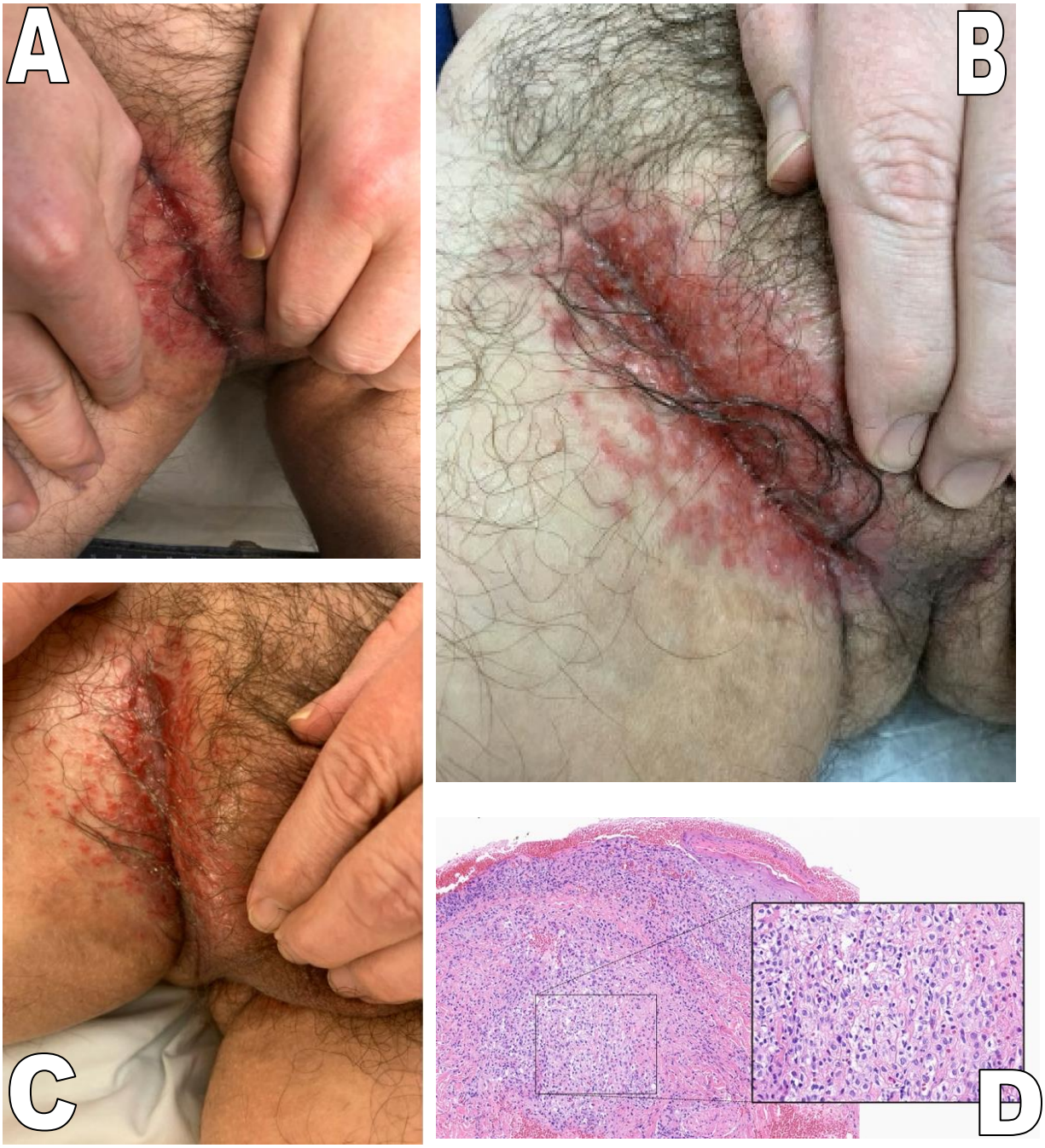

Figure 2
A. Right inguinal fold at the time of presentation
B. Right inguinal fold immediately after starting chemotherapy
C. Right inguinal fold 3 months after starting chemotherapy
D. Histopathology obtained from punch biopsy

ADULT MULTISYSTEMIC LANGERHANS CELL HISTIOCYTOSIS REQUIRING CHEMOTHERAPY

Discussion

- Langerhans cell histiocytosis is a rare clonal disorder caused by neoplastic proliferation of abnormal antigen-presenting cells (Langerhans cells). LCH most commonly presents from birth to age 15 years.
- The symptoms and clinical findings depend on the organ and extent of involvement. The histologic findings of LCH can be variable, but the primary lesion is granulomatous with eosinophils, macrophages, T cells and multinucleated cells. LCH can be classified into three main categories: single-system unifocal, single-system multifocal, or multisystem. Little is known about optimal chemotherapy regimen for adult multisystemic LCH. Prognosis is related to age of onset and number of organs involved.
- This disease demonstrates characteristics of abnormal reactive processes as well as neoplastic processes.
    - In about 75% of patients, there are mutually exclusive somatic activating mutations of BRAF, V600E and MAP2K1, which supports neoplastic origin of the disease.
- The presentation and prognosis of LCH is highly variable.
    - Initial presentation of LCH may affect the skin.
    - Any organ can be affected, with most frequently involved organs being bones (80%), skin (33%), and pituitary (25%), liver, spleen, hematopoietic system and lungs (15% each), lymph nodes (5–10%), and CNS (2–4%).
- Medical conditions associated with LCH: diabetes insipidus, growth failure, delayed puberty, tooth loss, mandibular bone loss, hearing loss, secondary cancers, neurologic/cerebellar effects, liver disease, and pulmonary fibrosis.
- Differential diagnosis includes the following:
    - *Candida* infection, malignant histiocytosis, sarcoidosis, eczema, contact dermatitis, seborrheic dermatitis, psoriasis, lichen planus

Teaching Points

- The spectrum of clinical presentations of LCH results in frequent misdiagnosis and presentation of patients to a variety of specialty providers. Therefore, it is critical to be aware of LCH manifestations in the skin, bones, CNS and other organ systems.
- A thorough physical exam is important in diagnosing LCH. Investigation should include imaging to determine extent of systemic involvement. Oncology should be involved.
- Treatment for LCH depends on the extent of disease. For presentation limited to the skin, topical steroids can be used. For more widespread disease, systemic steroids and chemotherapy may be necessary. It is important to identify disseminated disease and treat it appropriately to reduce morbidity.
- Radiation is also an effective and safe therapy for local control of LCH.

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CASE 15

A 22-YEAR-OLD WOMAN WITH ACRAL AND BUCCAL EROSIONS

Patient

AF is a 22-year-old African American woman

Presenters

Alice Tan, MSIII
Isabella Plumptre, MBBS
Karen Wiss, MD

History

A previously healthy woman presented to the ED with worsening bullae and erosions of her hands, feet, buccal and genital mucosa in the setting of a three month 60 lb unintentional weight loss. She also had a 6 month history of hyperpigmented papules and plaques on her hands, elbows and postauricular skin, consistent with lichen planus on an outside biopsy. She denied any ocular, respiratory, or GI symptoms.

Past Medical History: None.

Medications: No regular medications. Treated prior to presentation with prednisone taper, doxycycline and acyclovir, without improvement.

Physical Examination

Widespread erosions and ulcers at various stages of healing on bilateral hands and feet (palms, fingers, toes, web spaces), some with thick serosanguinous crusts.
Several intact vesicles and bullae on the volar forearms, some ruptured with overlying crusts. No ocular involvement. Superficial erosions on the vermillion lips, tongue, hard palate, gingivae and labia minora. Lichenoid papules on extensor knees.

Laboratory Data

- CBC: WBC + differential within normal limits, microcytic anemia. LDH elevated at 271
- Peripheral blood flow cytometry: polytypic B-cells, immunophenotypically normal T-cells, no immature myelomonocytic cells
- ELISA: positive for desmoglein 1, 3, BP180, BP230. Salt split skin with epithelial pattern IgG4. IIF: slightly positive for IgG4 BM monkey esophagus, negative rat and mouse bladder substrate, negative mouse heart and liver substrate testing
- Serum HHV8 PCR and IgG negative

Histopathology

1) **Forearm bulla** H&E: Suprabasilar cleft with apoptotic keratinocytes, eosinophilic spongiosis and superficial perivascular lymphocytic infiltrate with scattered eosinophils. DIF: linear to granular BMZ deposition of C3, IgG, IgM. No IgA or fibrinogen deposition. No significant intercellular fluorescence noted.

2) **En-block abdominal resection**: Proliferation of chronic inflammatory cells with areas of stromal fibrosis and hyalinization consistent with stroma–rich variant of unicentric Castleman disease, hyaline vascular type.

Imaging & Special Tests

CT chest/abdomen/pelvis: 21 x 8 x 10cm right retroperitoneal mass extending into the abdomen and sclerotic bony lesions of T11-L1
MRI brain: unremarkable
Ophthalmology exam: pending
Pulmonary function tests: pending

Treatment

- Exploratory laparotomy with en bloc resection of right retroperitoneal mass, right nephrectomy, right adrenalectomy and partial diaphragm resection
- Prednisone 1mg/kg with slow taper (4 months, currently at 10mg daily), with improvement in lesions. Started on mycophenolate mofetil 500mg BID with plan to continue steroid taper.
- Sucralfate and Magic Mouthwash for oral erosions
- Wound care with mupirocin ointment
- Occupational therapy

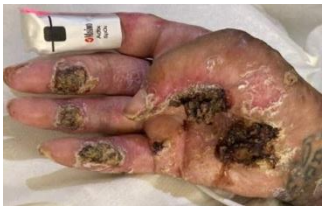

Figure 1: Erosions with thick crust of palm and fingers

CASE 15

A 22-YEAR-OLD WOMAN WITH ACRAL AND BUCCAL EROSIONS

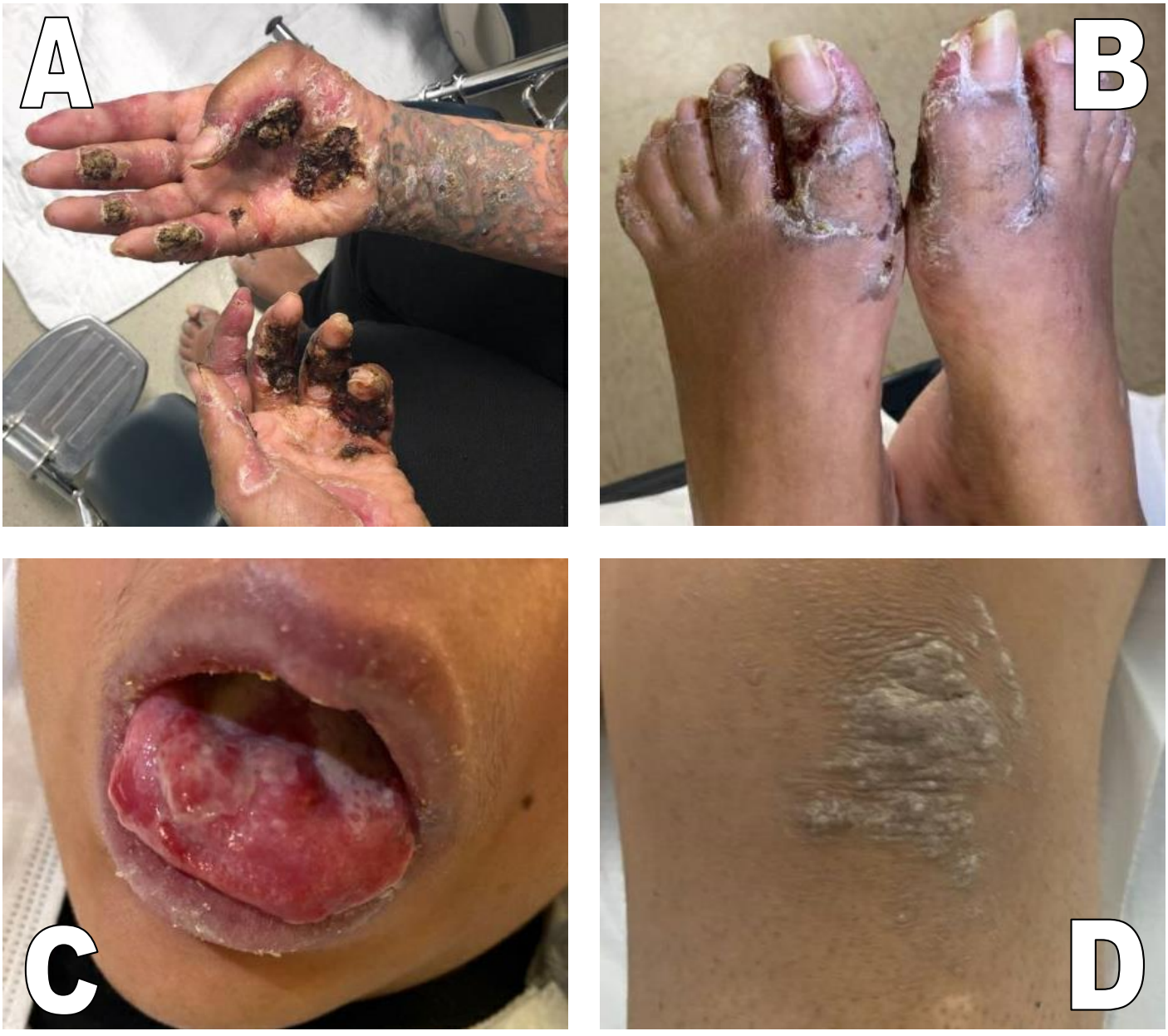

Figure 2 A-D: Erosions of A) palm and fingers, and B) toes, some with thick serosanguinous crusts. C) erosions of tongue and mucosal lips. D) lichenoid papules on extensor knee.

CASE 15

A 22-YEAR-OLD WOMAN WITH ACRAL AND BUCCAL EROSIONS

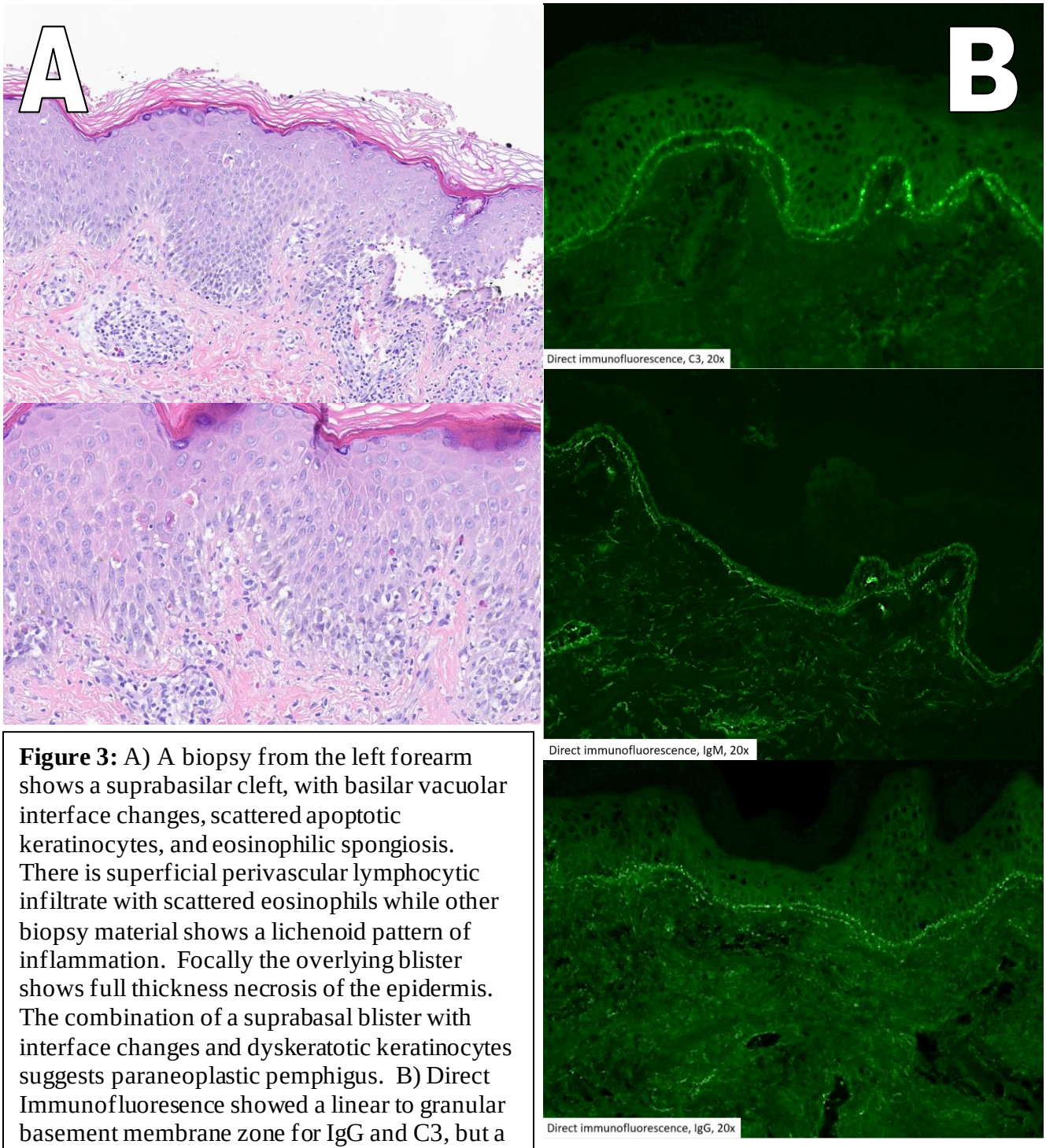

Figure 3: A) A biopsy from the left forearm shows a suprabasilar cleft, with basilar vacuolar interface changes, scattered apoptotic keratinocytes, and eosinophilic spongiosis. There is superficial perivascular lymphocytic infiltrate with scattered eosinophils while other biopsy material shows a lichenoid pattern of inflammation. Focally the overlying blister shows full thickness necrosis of the epidermis. The combination of a suprabasal blister with interface changes and dyskeratotic keratinocytes suggests paraneoplastic pemphigus. B) Direct Immunofluoresence showed a linear to granular basement membrane zone for IgG and C3, but a weak or focal intercellular pattern was not seen in this material.

PARANEOPLASTIC PEMPHIGUS

Discussion

- Paraneoplastic pemphigus (PNP) is a rare blistering skin condition associated with a variety of neoplastic processes, including non-Hodgkin lymphoma (39%), Castleman disease (18%, most common associated disease in children), chronic lymphocytic leukemia (18%), epithelial carcinomas (9%), thymoma (6%), and sarcoma (6%). The underlying neoplastic cause is unidentified in the majority (2/3) of patients at the time of PNP presentation.
- The mechanism of PNP involves IgG autoantibodies against multiple antigens including desmoglein 3 & 1 (leading to breakdown of keratinocyte adhesion and subsequent blister formation) and the plakin family (desmoplakin I + II, bullous pemphigoid antigen I, envoplakin, periplakin, and plectin; the significance of these autoantibodies is unclear).
- Clinical manifestations of PNP include severe stomatitis (usually the first presenting sign), pseudomembranous conjunctivitis, genital erosions, and polymorphous cutaneous lesions (resembling pemphigus vulgaris, bullous pemphigoid, lichen planus, erythema multiforme and graft-versus-host disease).
- Histopathologic findings are variable, but commonly include suprabasal acantholysis, keratinocyte necrosis, and a lichenoid interface dermatitis. DIF may demonstrate IgG and/or C3 in an intercellular staining pattern. Indirect immunofluorescence with rat bladder substrate has the highest sensitivity + specificity for diagnosis.
- Differential diagnosis:
    - Pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, lichen planus, graft versus host disease, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, IgG-4 disease, epidermolysis bullosa acquisita.
- Treatment is challenging and there are no consensus guidelines. The mainstay is treatment of the underlying neoplastic process. Systemic steroid therapy ± steroid sparing immunosuppressive agents (e.g. mycophenolate mofetil) are first line; rituximab or intravenous immunoglobulin (IVIG) can also be considered. Stomatitis is often recalcitrant and typically requires treatment with multiple agents.
- If the underlying tumor is resectable, then lesions of PNP are expected to resolve within the following months. Otherwise, the prognosis of PNP is poor.
- Complications of PNP include bronchiolitis obliterans (the major cause of mortality), infection and sepsis, blindness, malnutrition secondary to reduced oral intake from painful erosions, and myasthenia gravis.

Teaching Points

- The majority of PNP cases present before an underlying neoplastic diagnosis is recognized. Screening for underlying neoplasia includes CBC, LDH, protein electrophoresis, CT of chest/abdomen/pelvis and endoscopy/colonoscopy.
- Treatment of PNP includes management of the underlying malignancy, systemic steroids and additional steroid sparing immunosuppressive therapies.
- Baseline pulmonary function tests are essential due to risk of life-threatening pulmonary involvement (bronchiolitis obliterans); any new pulmonary symptoms (dyspnea, cough) should be urgently evaluated.
- Refer to ophthalmology given long term ocular sequelae of PNP and significant risk of visual impairment.

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CASE 16

A 2-YEAR-OLD BOY WITH A PERSISTENT VESICULOBULLOUS ERUPTION IN A "CROWN OF JEWELS" DISTRIBUTION

Patient

JD is a 6-year-old Caucasian boy.

Presenters

Gabriella Paquette, MSIII
Isabella Plumptre, MBBS
Karen Wiss, MD

History

An otherwise healthy 6-year-old boy initially presented at age 2 with 5 weeks of pruritic vesicles, bullae, papules and crusted erosions on the extremities, scalp, and periorificial regions, later spreading to the trunk. Prior to presentation, he received cephalexin for presumed bullous impetigo without improvement.

Past Medical History: Asthma

Allergies: Amoxicillin

Medications: Age 2 – Albuterol inhaler, Benadryl, hydroxyzine, and mometasone ointment

Physical Examination

Age 2: Perioral papules coalescing into plaques with few vesiculopustules at the periphery. No lesions of oral mucosa. On the trunk, upper and lower extremities, scattered vesicles, bullae, and crusted erosions, some in a "crown of jewels" distribution. Relative sparing of the palms + soles. No grouping of vesicles. No surrounding erythema.

Laboratory Data

- Aerobic culture: no growth
- PCR swab (skin) negative for enterovirus, herpes simplex virus 1+2, and varicella zoster virus

Histopathology

Neutrophil rich subepidermal vesicular dermatitis, impetiginized. PAS stain negative. Direct immunoflourescence is strongly positive for IgA and weak granular staining for IgM, both linear along the dermoepidermal junction (IgG, C3 and fibrinogen negative).

Treatment

Currently well controlled on:

- Cephalexin (started at presentation, initial dosing 250mg twice daily, now tapered to 250mg daily)
- Dapsone 2mg/kg/day PO divided twice daily (started at presentation)

Required multiple courses of prednisolone 1mg/kg PO for treatment of flares. Noted significant improvement after starting IVIG (received 5 infusions to date, last 18 months ago).

Course has been complex and failed multiple therapies, including:

- Erythromycin 200mg PO twice daily (1 week treatment duration)
- Colchicine 0.3mg PO daily (2 months)
- Mycophenolate mofetil 250mg PO twice daily (3 months)
- Cyclosporine 5mg/kg PO divided twice daily (3 months)
- Rituximab 375mg/m^2 IV (two infusions)
- Methotrexate 15mg PO once weekly (9 months)

Referrals:

- Pediatric gastroenterology (secondary to slow growth in the setting of chronic systemic steroid therapy)
- Pediatric ophthalmology and endocrinology (secondary to chronic systemic steroid therapy)

Fig. 1: crusted erosions in a 'crown of jewels' distribution across the thigh

CASE 16

A 2-YEAR-OLD BOY WITH A PERSISTENT VESICULOBULLOUS ERUPTION IN A "CROWN OF JEWELS" DISTRIBUTION

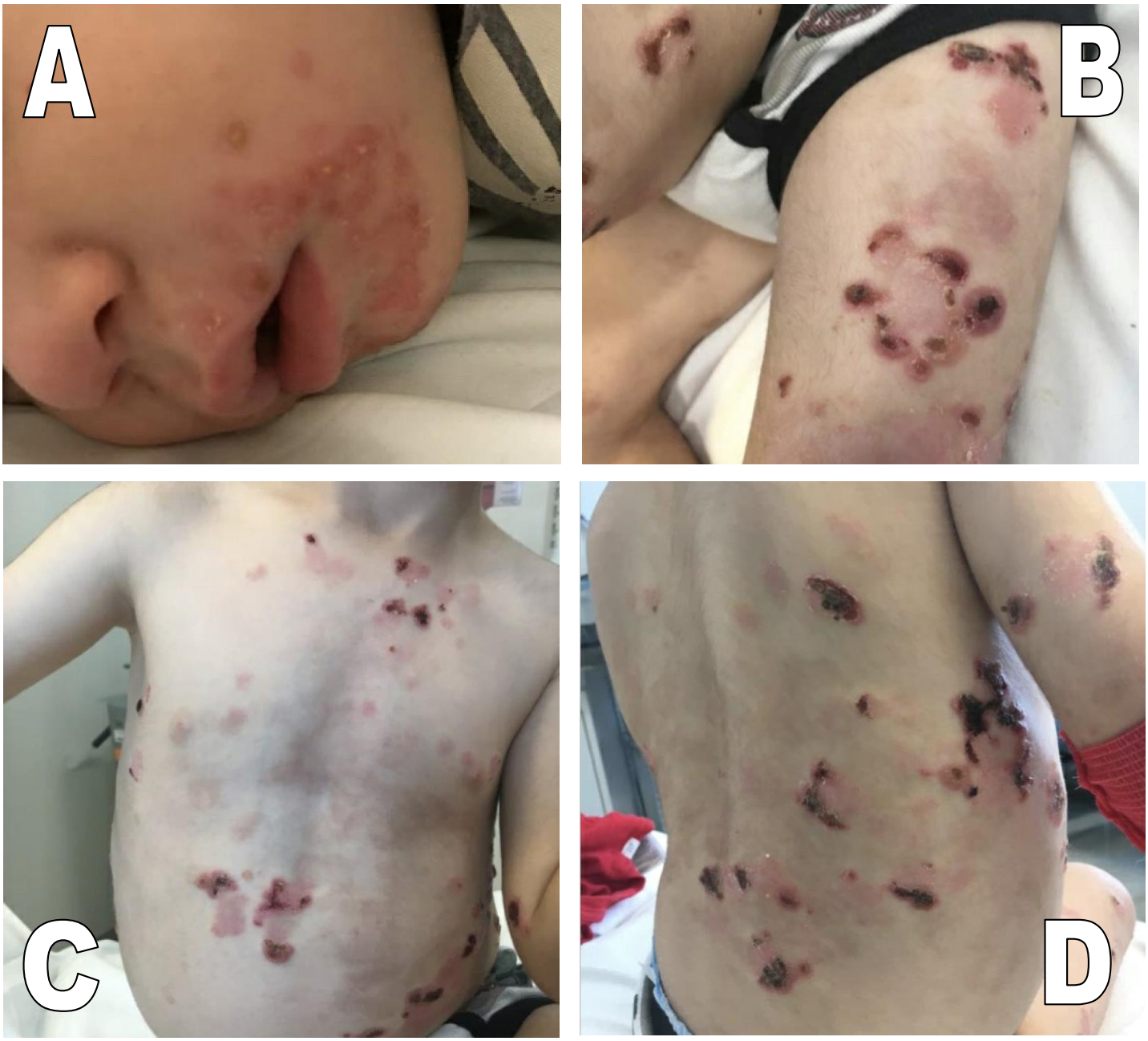
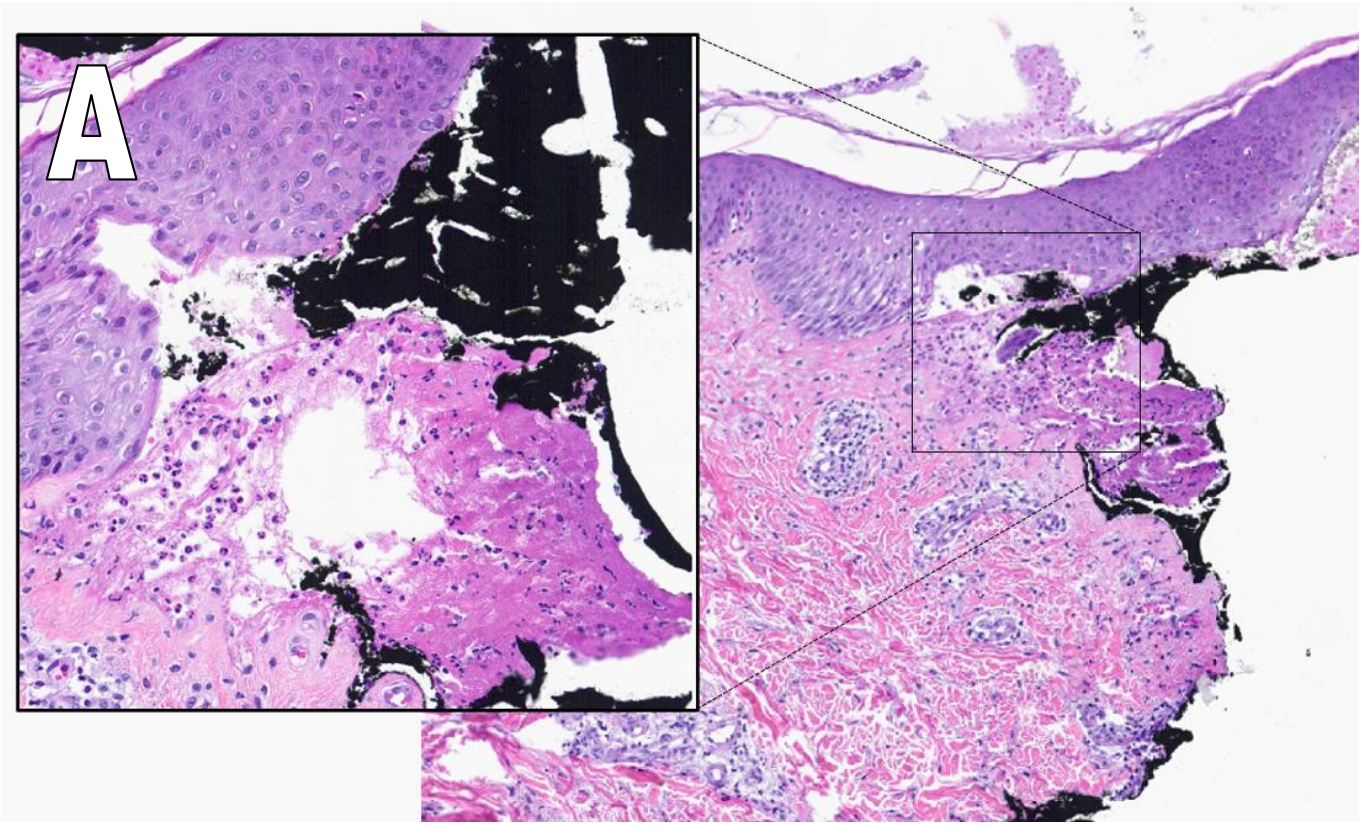


Fig. 2 A-D. A) Perioral crusted papules. B-D) crusted vesicles, bullae and erosions, some in a "crown of jewels" distribution, across the trunk and extremities.

CASE 16

A 2-YEAR-OLD BOY WITH A PERSISTENT VESICULOBULLOUS ERUPTION IN A "CROWN OF JEWELS" DISTRIBUTION



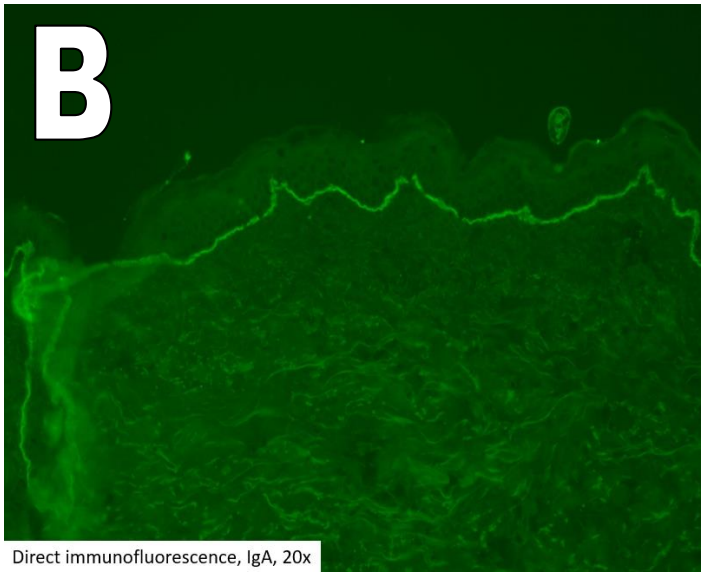


Fig. 3 A) The biopsy demonstrates the edge of subepidermal blister with abundant neutrophils within the blister. There is mild perivascular lymphocytic and neutrophilic interstitial inflammation in the superficial dermis. B) Direct immunofluorescence shows strongly positive linear IgA and weakly positive granular IgM staining along the dermoepidermal junction. IgG, C3 and fibrinogen are negative.

CHRONIC BULLOUS DISEASE OF CHILDHOOD

Discussion

- Chronic Bullous Disease of Childhood (CBDC), also known as Linear IgA Bullous Dermatosis (LABD) when affecting adults, is a rare subepidermal blistering disorder caused by IgA autoantibodies targeting LAD-1 and LADB97. These antigens are derived from BPAG2 (bullous pemphigoid antigen 2).
- The clinical presentation of CBDC is classically annular tense vesicles or bullae, also known as a "crown of jewels" or "string of pearls" distribution, on the face, trunk, buttocks and thighs of a pre-school age child. Bullous lesions may be on a background of normal-appearing skin or urticarial plaques, and vesiculopustules may be present at the periphery. In adults, and less commonly children, there may be involvement of mucous membranes including oral, ocular, nasal and esophageal mucosa.
- A subset of cases are drug-induced. Vancomycin is the most common triggering medication, although many others have been associated including captopril, NSAIDS, penicillins, cephalosporins, and phenytoin.
- The gold standard for confirming the diagnosis of CBDC is direct immunofluorescence, demonstrating linear IgA deposition at the basement membrane zone of perilesional skin. Indirect immunofluorescence reveals epidermal staining on salt-split skin.
- The majority of childhood cases tend to remit spontaneously over 2-4 years. Drug-induced cases usually resolve within weeks of discontinuing the triggering medication.
- CBDC typically responds rapidly to dapsone as a first-line treatment. Second line agents include colchicine and sulfapyridine. Short courses of systemic steroids may be required to control flares. Management also includes wound care and monitoring for mucosal involvement which requires urgent referral to the relevant subspecialists. Severe, treatment resistant cases may require additional immunosuppressive therapy, such as methotrexate, mycophenolate mofetil, etanercept, IVIG, and rituximab. Evidence for treatments is from case reports/series; there are no randomized controlled trials or consensus guidelines on this topic.
- Differential diagnosis:
    - dermatitis herpetiformis, bullous pemphigoid, bullous impetigo, coxsackie infection, herpes simplex virus infection, mucous membrane pemphigoid, epidermolysis bullosa acquisita, erythema multiforme, and bullous fixed drug eruption

Teaching Points

- Chronic bullous disease of childhood presents with tense bullae and vesicles in a "crown of jewels" distribution and may be associated with mucosal involvement.
- The diagnosis of CBDC/LABD is confirmed on direct immunofluorescence, with linear deposition of IgA at the basement membrane zone.
- CBDC typically responds rapidly to dapsone. However, some cases can be recalcitrant, necessitating additional immunosuppressive therapy such as systemic steroids, IVIG or rituximab. Mucosal involvement should prompt urgent referral to the relevant specialist (e.g. ophthalmology, gastroenterology).

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CASE 17

A 40-YEAR-OLD MAN WITH AN INDURATED PLAQUE ON THE LOWER LIP

Patient

RG is a 40-year-old Brazilian man.

Presenters

Sina Foroutanjazi, MSIV
Steven Krueger, MD
Mark Scharf, MD

History

A 40-year-old man with a history of oral herpes simplex virus (HSV) presented with a painful rash on the lower lip for three months. He was living in Brazil when the rash began. He reported small blisters that quickly spread to involve the entire lip. He also noticed small “pimples” on his abdomen and temple. He had recently completed two courses of amoxicillin/clavulanate, doxycycline, and acyclovir for a presumed diagnosis of impetigo and oral herpes.

Past Medical History: Oral HSV

Family History: Unremarkable

Allergies: No known allergies

Medications: Amoxicillin/clavulanate, doxycycline, valacyclovir, mupirocin, ibuprofen

Physical Examination

On the lower lip extending onto the chin, there is a large, tender, ulcerated plaque with an overlying thick yellow crust, purulent discharge, and a pink, indurated border. There are smaller pink plaques with central crust on the right temple and left abdomen. There is no cervical lymphadenopathy or hepatosplenomegaly.

Laboratory Data

- Tissue culture positive for polymicrobial growth

Histopathology

Punch biopsies of the lip and abdomen showed ulceration with a plasmacytic infiltrate involving the superficial and deep dermis. Numerous parasitized macrophages were present. The parasites were 2-4 µm in size, had eccentrically located kinetoplasts, and localized to the periphery of the cytoplasm (the "marquee sign"). The organisms stained positive for Giemsa and negative for Grocott's Methenamine Silver (GMS) and Periodic acid–Schiff stain (PAS) stains.

Treatment

- Miltefosine 50 mg PO TID for 28 days

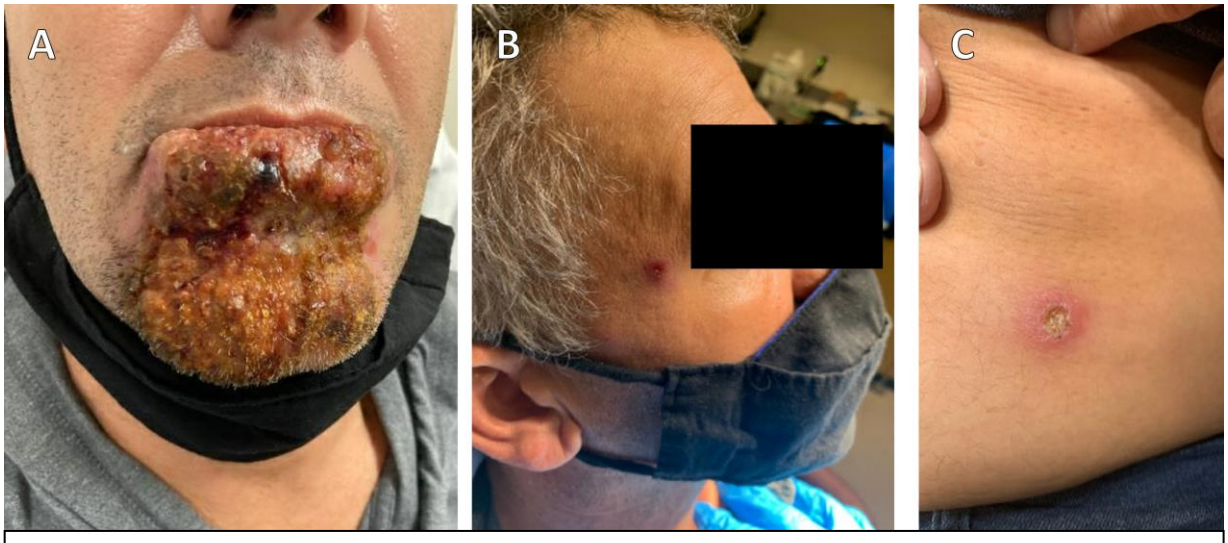

Fig. 1 A-C: Crusted plaques on the lower lip, temple, and abdomen

CASE 17

A 40-YEAR-OLD MAN WITH AN INDURATED PLAQUE ON THE LOWER LIP

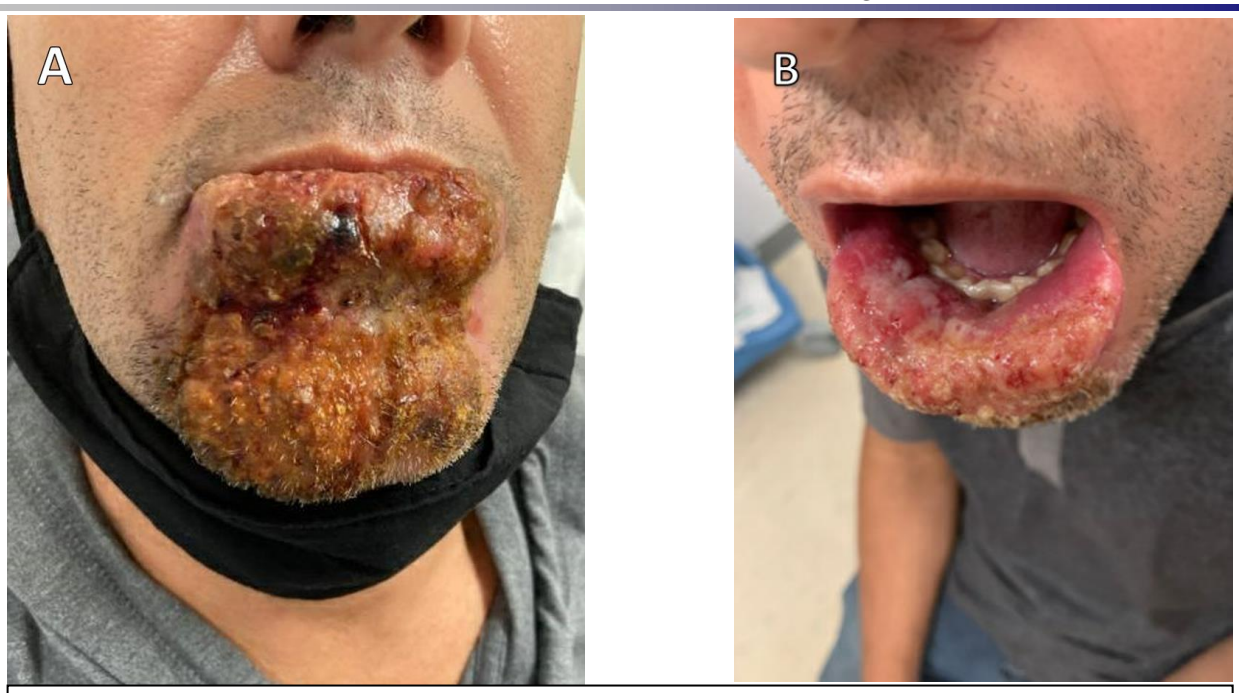

Fig. 2 A, B: Crusted plaque on the lower lip, with superficial erosions of the mucosal surface

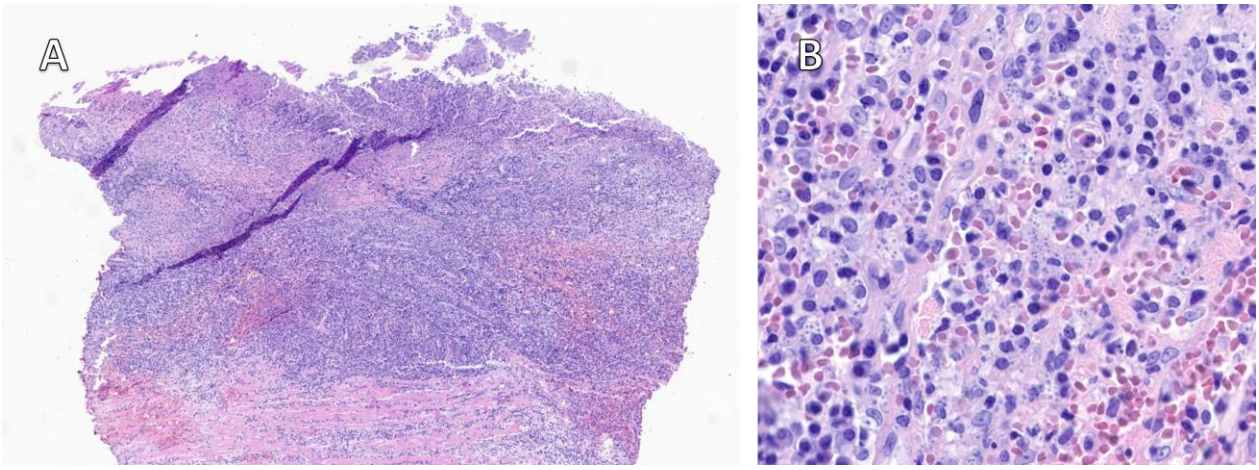

Fig. 3 A, B: Biopsies from the lower lip and abdomen show similar findings. On the lip, there is a lymphoplasmacytic and histiocytic infiltrate that extends from an ulcerated surface into underlying skeletal muscle. There are abundant phagocytized macrophages with organisms that are 2-4 µm in size, have eccentrically located kinetoplasts, and show peripheral cytoplasm localization. Giemsa highlights these organisms and they are negative for GMS and PAS. These findings are sufficient for a diagnosis of leishmaniasis.

CUTANEOUS LEISHMANIASIS

Discussion

- Leishmaniasis is a tropical disease caused by an intracellular parasite that is transmitted by the bite of a sandfly.
- New World cutaneous leishmaniasis (NWCL) occurs in Central and South America, especially in Brazil and Peru, while Old World cutaneous leishmaniasis (OWCL) is more common in Africa, Asia, and the Middle East.
- Our patient's history of immigration from Brazil points to a diagnosis of NWCL, likely with *L. braziliensis*. However, OWCL has also been reported in South America. We contacted the CDC shortly after making the diagnosis, and we are now working with a lab at McGill University to obtain speciation data for this case.
- Early NWCL begins with erythema at the site of a sandfly bite, which evolves over the course of weeks to months into papules, nodules, ulcers, or plaques. It can mimic erysipelas, impetigo, sporotrichosis, paracoccidioidomycosis, leprosy, cutaneous tuberculosis, syphilis, and keratinocyte carcinoma.
- Long-standing NWCL can involve mucosal surfaces, which can lead to ulceration and nasal septal perforation. Our patient had superficial erosions of the mucosal lip and is therefore being referred to otolaryngology for endoscopic evaluation of the oropharynx.
- Diagnostic methods include microscopic examination of Giemsa-stained biopsy specimens, identifying amastigotes under light microscopy, obtaining a parasitic culture, and identifying parasitic DNA with PCR.
- Treatment of NWCL depends on drug sensitivity, accessibility, and the presence of mucosal involvement, which necessitates systemic treatment. Local therapies can be considered for clinically simple skin lesions.
- Parenteral treatment options include amphotericin B, sodium stibogluconate, meglumine antimonate, and pentamidine. Miltefosine is an effective, convenient, and widely available oral treatment option.

Teaching Points

- Providers should have a high index of suspicion for cutaneous leishmaniasis in patients traveling from endemic areas, especially Brazil, Peru, North Africa, and the Middle East.
- Cutaneous leishmaniasis can mimic various conditions and may involve mucosal surfaces or internal organs.
- Diagnosis can be made with histopathological assessment of Giemsa-stained biopsy specimens, PCR evaluation of parasitic DNA, and parasitic culture. Speciation data may help to guide management.
- Cutaneous leishmaniasis with mucosal involvement requires systemic treatment such as with intravenous amphotericin B, sodium stibogluconate, or meglumine, or alternatively with oral miltefosine.

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CASE 18

A 60-YEAR-OLD WOMAN WITH ERYTHEMATOUS NODULES OF THE EXTREMITIES

Patient

RL is a 60-year-old Hispanic woman.

Presenters

Jatin Narang, MSIV
Sarah Servattalab, MD
Mehdi Rashighi, MD

History

A chronically-immunusuppressed 60-year-old woman with a known history of poorly-controlled rheumatoid arthritis (RA) presented with a 2-year history of worsening fatigue, joint pain, and intermittent erythematous nodules on her forearms, fingers, lower legs, and toes that were previously attributed to accelerated rheumatoid nodulosis. The lesions had become more painful over the last 3 months. RLis a homemaker and denies any recent travel out of the U.S., exposure to animals or fish, farming or gardening.

Past Medical History: RA for years, previously on methotrexate and TNF-α inhibitors, and a history of erythema induratum of Bazin secondary to latent tuberculosis seven years ago (completed a full course of antituberculosis treatment)

Medications: Abatacept and methylprednisolone

Physical Examination

There are multiple pink to violaceus firm papules and fluctuant nodules of varying sizes on the bilateral upper and lower extremities. In addition, there are ill-defined pink, erythematous patches on the lower abdomen and thighs.

Laboratory Data

- CBC without leukocytosis but with an absolute neutrophil count of 7570 cells/uL (1600–7500 cells/uL), an absolute lymphocyte count of 600 cells/uL (500-3400), a hemoglobin of 9.8 g/dL (11.7–15.5 g/dL), hematocrit 31.3% (35-46%), platelets 47400 platelets/uL (14000-44000 platelets/ul)
- BMP normal aside from glucose elevated at 259 mg/dL (70-99 mg/dL)
- CRP elevated at 50.3 mg/L (<10 mg/L)
- Total bilirubin 1.4 mg/dL (0.3 – 1.2 mg/dL)

Histopathology

Two punch biopsies of distinct nodules from both right and left forearm showed transected subcutaneous neutrophil abscesses, with dermal fibrosis, edema and perivascular and interstitial lymphohistiocytic infiltrates. Periodic acid-shift (PAS) and Gram stains were negative for organisms. Tissue cultures did not grow any organisms.

Repeat deep punch biopsies from four separate lesions on both arms and legs showed granulomatous and suppurative dermatitis with central necrosis. Within the necrotic foci of the dermis of only one out of four biopsies taken from left elbow, rare bacilli were highlighted by acid-fast bacilli (AFB) and Fite stains. PAS and Gram stains were negative for definitive organisms. Three additional biopsies were obtained from the left forearm for tissue culture, and after eight weeks only one of them grew *Mycobacterium marinum*.

Of note, upon further questioning, the patient vaguely recalled sustaining a minor trauma to her fingers after being bitten by a crab at a beach four year prior.

Treatment

- Promptly discontinued abatacept and methylprednisolone
- Empirically started clarithromycin, ethambutol, and rifampin
- Tailored to clarithromycin, moxifloxacin, and rifampin after susceptibility testing

CASE 18

A 60-YEAR-OLD WOMAN WITH ERYTHEMATOUS NODULES OF THE EXTREMITIES

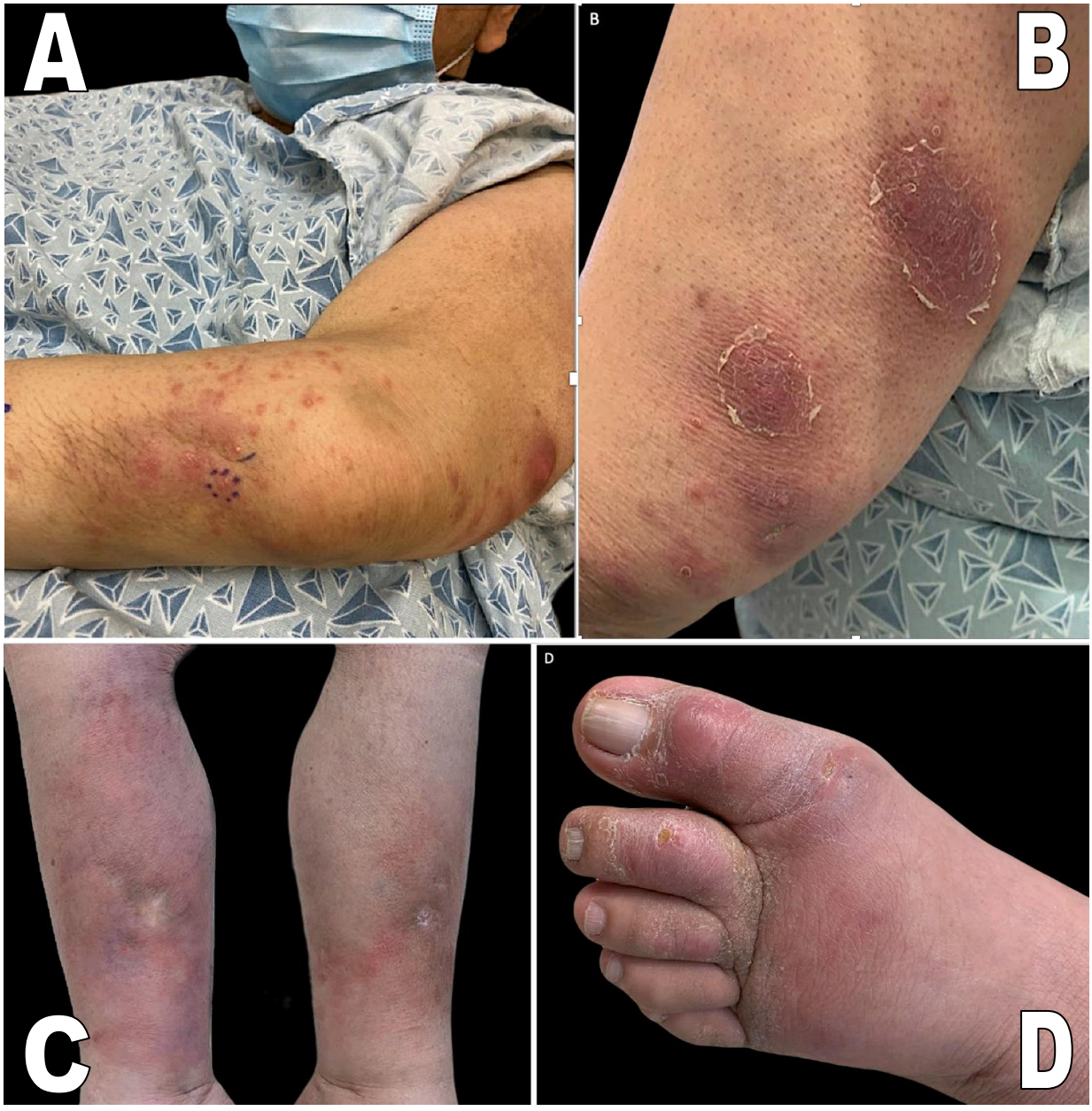

Figure 1: A) Erythematous and fluctuant nodules on the bilateral upper extremities. **B)** Nodular area of initial and follow-up biopsy of the patient's left forearm. **C)** Ill-defined pink erythematous patches on the bilateral thighs. **D)** Violaceous, fluctuant nodule on the dorsal great toe.

CASE 18

A 60-YEAR-OLD WOMAN WITH ERYTHEMATOUS NODULES OF THE EXTREMITIES

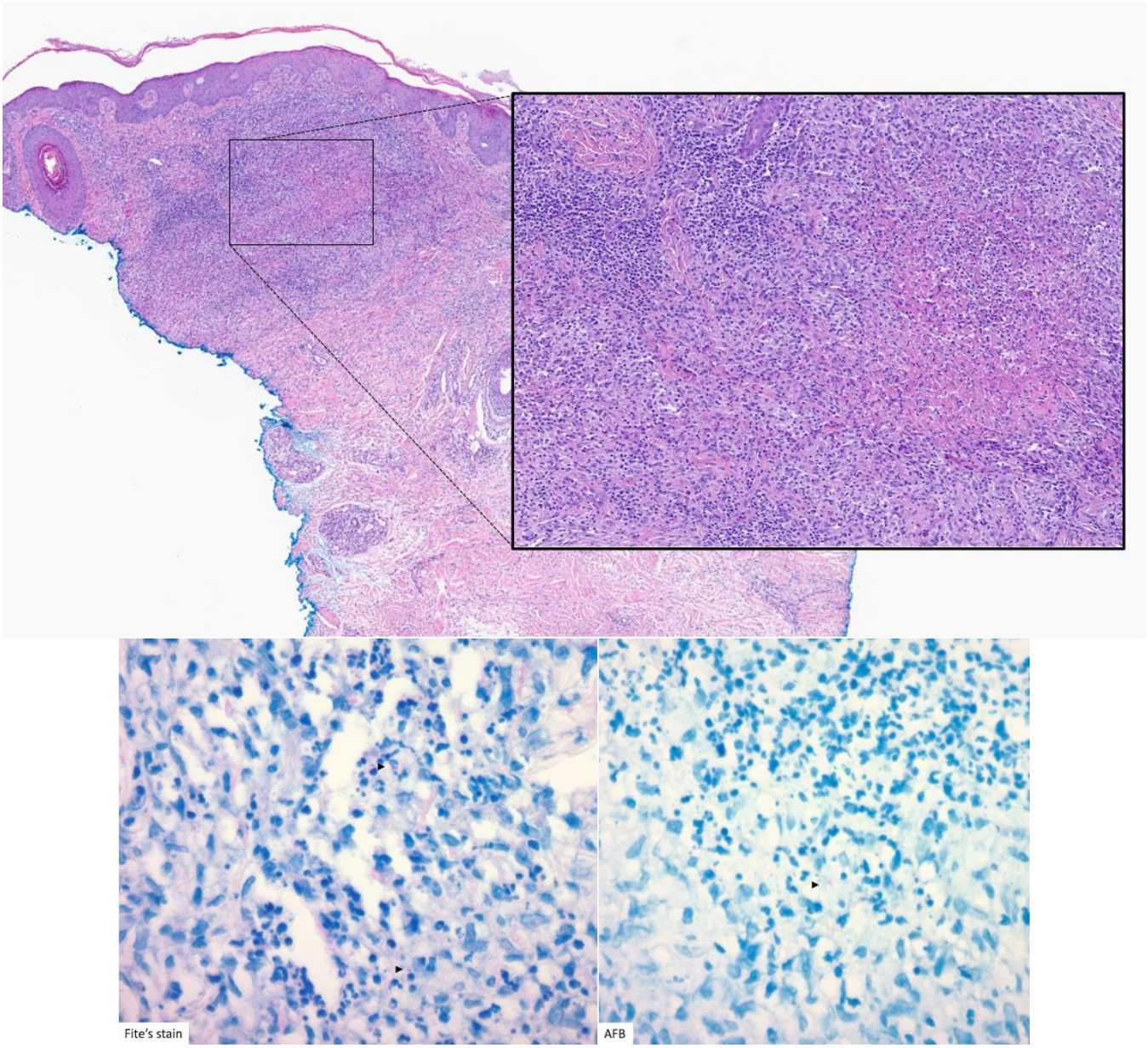

Figure 2: Multiple biopsies were performed showing varying degrees of granulomatous inflammation. A biopsy from the left forearm showed dense granulomatous and suppurative inflammation involving the superficial and mid-dermis. Some of the granulomas show central necrosis. AFB and Fite stains showed rare bacilli within the granulomatous inflammation.

MYCOBACTERIUM MARINUM INFECTION MIMICKING RHEUMATOID ARTHRITIS FLARE

Discussion

- *Mycobacterium marinum* infection also known as "fish tank" or "swimmer's granuloma" occurs through injured skin that is exposed to a contaminated aqueous environment. This non-tuberculous mycobacteria (NTM) is present in both freshwater and saltwater. Infection annual incidence is 0.27 per 100,000.
- Risk factors for *M. marinum* include working in wet fields, participating in aquatic sports, and cleaning aquariums.
- Infections initially present as a solitary violaceous plaque or nodule at site of trauma 2-3 weeks after inoculation. Nodules may be crusted, ulcerated, or verrucous. Occasional lymphocutaneous spread may occur.
    - Deeper infection including osteomyelitis and tenosynovitis have been described with delayed treatment.
- The constellation of joint pain, nodules, and granulomatous histopathologic findings of *M. marinum* infection can often be confused for rheumatoid arthritis features. AFB stains and culture should be requested if *M. marinum* is on the differential.
    - There is an increased risk of NTM infection and worsening of existing infections in patients on immunosuppressants, especially TNF-α inhibitors.
    - Key differentiators between *M. marinum* infection and rheumatoid nodules include asymmetrical presentation, draining nodules, and poor response to immunosuppressants.
- There is no consensus on the regimen and duration of therapy for *M. marinum* infections. Treatment should include two agents (rifampin, clarithromycin, ethambutol, doxycylcine, or moxifloxacin) for 6-12 months.
    - Surgical debridement may be required if not responsive to antibiotics.
- *M. marinum* should be on the differential in patients with poorly healing nodular lesions not responding to antibiotics. Other things on differential diagnosis include:
    - Fungal cutaneous nodular infections like blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis.
    - Cutaneous infections with lymphatic distribution including leishmaniasis, nocardiosis, and sporotrichosis.

Teaching Points

- Instruct patients on limiting exposure risk by avoiding aquatic environments, covering abrasions with waterproof bandages, and wearing gloves when cleaning aquariums.
- High clinical suspicion for NTM infections is warranted in patients with atypical presentations of inflammatory arthritis or in patients with poor response to immunosuppressive therapy.
- AFB studies are rarely positive in *M. marinum* infections as the number of mycobacteria in specimens is low leading to low specificity of staining and culture.
- If *M. marinum* is on the differential, repeated skin biopsies should be obtained for H&E and culture.
- The average time to diagnosis is 17 months. Prognosis is excellent if identified and treated early.

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CASE 19

A 34-YEAR-OLD WOMAN WITH CIRCULAR ATROPHIC LESIONS ON THE BREASTS

Patient

AU is a 34-year-old pregnant African American female.

Presenters

Isabella DiMare, RN
Kelly Flanagan, MSIV
Steven Krueger, MD
John Harris, MD, PhD
Nikki Levin, MD, PhD

History

A 34-year-old pregnant African American female presented with asymptomatic, hyperpigmented, circular, depressed lesions on the breasts that appeared around the same time that she received intramuscular penicillin for a diagnosis of late latent syphilis, based on routine prenatal testing. She denied any preceding rash over the affected areas.

Past Medical History: Primary syphilis diagnosed three years prior, with possible chancre on right breast at site of potential exposure; treated with penicillin without cutaneous reaction.

Family History: Unremarkable

Allergies: No known allergies

Medications: None

Physical Examination

Skin exam revealed numerous hyperpigmented, circular depressions with overlying epidermal wrinkling over the bilateral breasts.

There was a large, hyperpigmented plaque with central xerotic scale on the right lateral breast.

Laboratory Data

- Rapid plasma reagin (RPR) reactive (1:8)
- HIV negative

Histopathology

A punch biopsy from the breast revealed a thin epidermis with a fibrotic dermis showing increased ectatic perpendicularly arranged superficial vessels. Within the deep dermis, there were remnants of a disrupted hair follicle consisting of loose hair shafts, perifollicular fibrosis, and a granulomatous infiltrate. An elastic stain showed focal loss of elastic tissue centered above the ruptured follicle. A Treponema stain was negative.

Treatment

- Follow-up with external providers for continued management of latent syphilis
- Cosmetic treatments are being considered after delivery

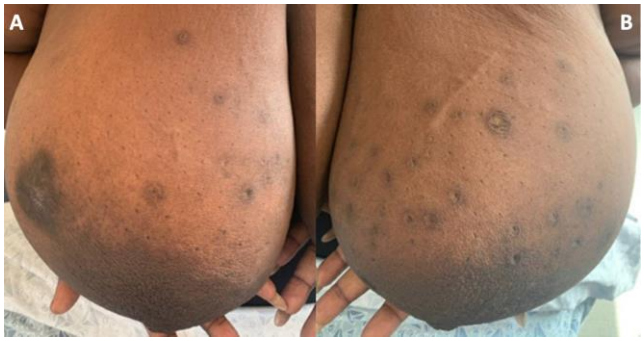

Figure 1. Atrophic hyperpigmented macules on right breast (A) and left breast (B).

CASE 19

A 34-YEAR-OLD WOMAN WITH CIRCULAR ATROPHIC LESIONS ON THE BREASTS

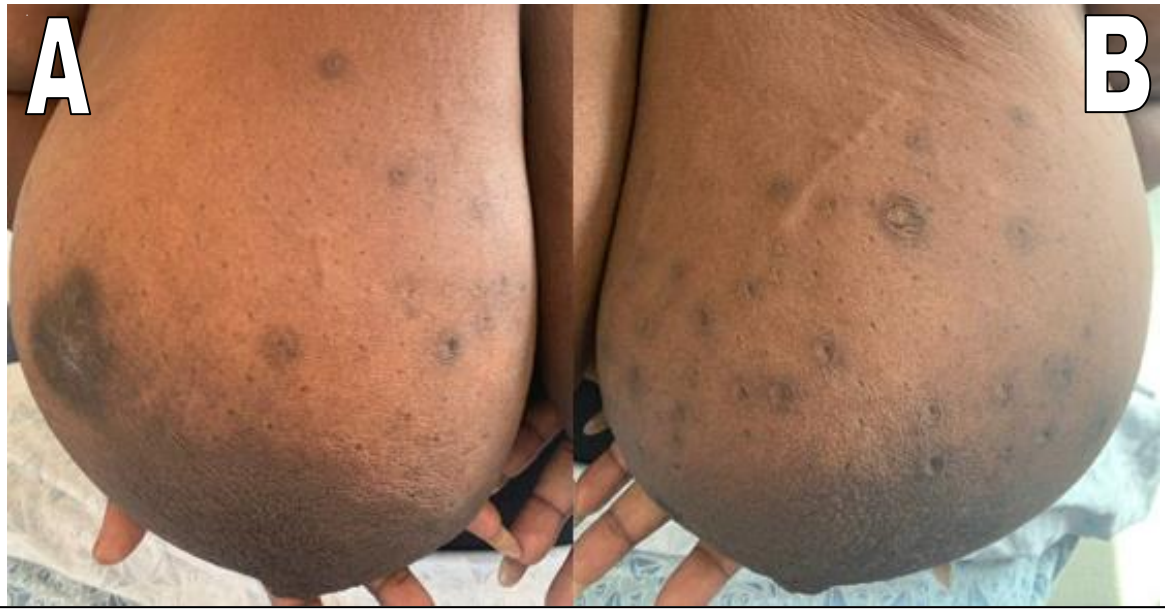

Figure 1. Atrophic hyperpigmented macules on right breast (A) and left breast (B).

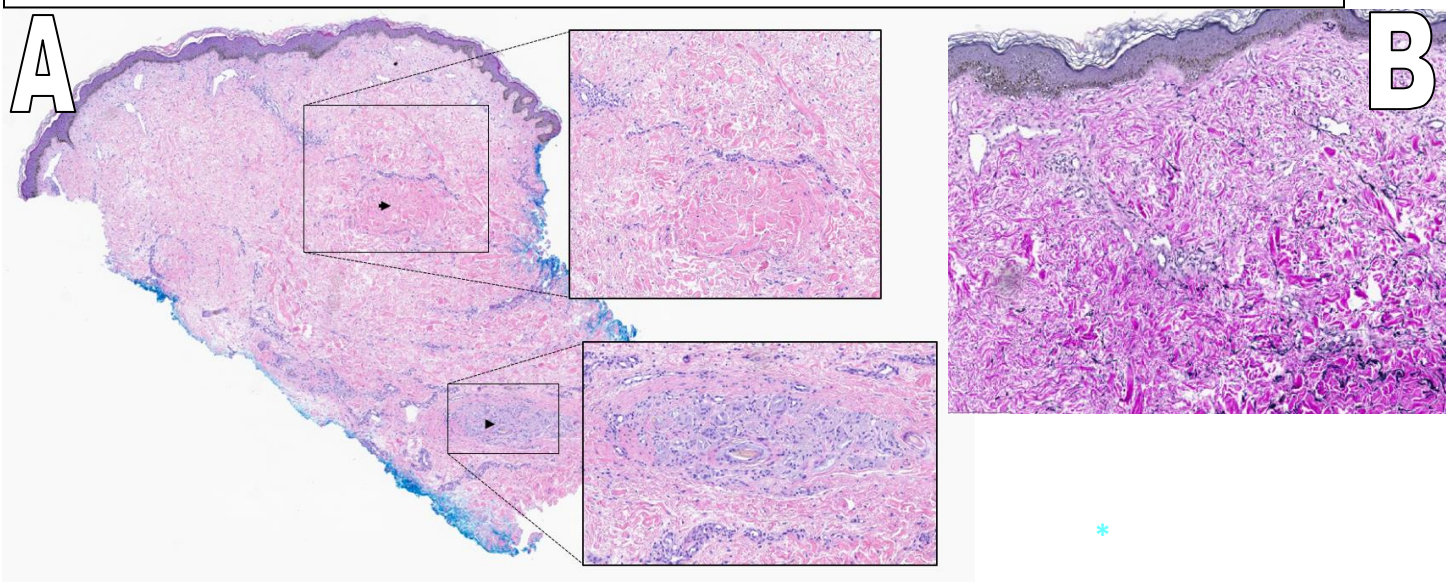

Figure 2. Biopsy demonstrates an atrophic epidermis with dermal fibrosis involving the mid and deep dermis (A). Scar-like changes are appreciated with remnants of a disrupted hair follicle and granulomatous inflammation. There is perifollicular fibrosis outlining the residual follicle. There is localized reduction of elastic tissue adjacent to the follicle tract (B). An immunostain for spirochetes is negative. The features, in the setting of characteristic clinical lesions, are suggestive of anetoderma or anetoderma-like scar.

PRIMARY ANETODERMA ASSOCIATED WITH LATENT SYPHILIS INFECTION

Discussion

- Anetoderma is a rare, benign disorder that clinically presents as well-circumscribed, skin-colored atrophic macules and patches with a wrinkled appearance on the trunk and/or extremities. Lesions tend to bulge or herniate with palpation into sac-like protrusions.
- Histologically, anetoderma lesions demonstrate focal loss of elastic fibers in the superficial and mid-dermis. Histologic analysis may help to differentiate anetoderma from other elastolytic conditions.
- Primary anetoderma occurs in areas of skin that appear normal prior to the onset of atrophy.
- Secondary anetoderma occurs in areas of previous or current skin pathology, such as acne, insect bites, varicella, and syphilis.
- Pathogenesis is largely unknown; localized loss of elastic fibers may result from defective elastin synthesis, increased activity of elastolytic enzymes, or autoimmune-mediated destruction of fibers.
- Anetoderma has been associated with numerous infections, medications, and autoimmune conditions, including lupus erythematosus, autoimmune thyroiditis, and anti-phospholipid antibody syndrome.
- **Anetoderma and Syphilis:**
  - Interestingly, syphilis was noted to be one of the most common causes of secondary anetoderma in the 1930s, with lesions generally developing during the early secondary stage of syphilis infection.
  - In modern literature, few case reports have associated anetoderma with syphilis. In one case of a patient with HIV and active secondary syphilis, anetoderma lesions developed during treatment with intravenous penicillin. In another case, a patient without HIV or active syphilis developed primary anetoderma two years after treatment of primary syphilis with penicillin.

Teaching Points

- As the incidence of syphilis is increasing, dermatologists should be aware of its association with anetoderma. Recent case reports demonstrate that anetoderma can present during treatment of active syphilis or years after a resolved infection.
- Providers should consider inquiring about sexually transmitted infections and obtaining RPR titers in patients presenting with anetoderma.
- Biopsy may help to confirm a diagnosis of anetoderma and rule out other elastolytic conditions.
- While there is no curative treatment for anetoderma, cosmetic treatments such as resurfacing lasers, radiofrequency devices, biostimulatory fillers, focal chemical peels, and dermabrasion may be beneficial.

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CASE 20

A 27-YEAR-OLD WOMAN WITH HYPERPIGMENTATION, EDEMA, AND NODULARITY OF THE LOWER EXTREMITIES

Patient

MM is a 27-year-old woman.

Presenters

Afsheen Sharifzadeh, MD
Mary Awad, MD
Leah Belazarian, MD

History

A 28-year-old woman with Graves disease who previously underwent thyroidectomy presented with progressively worsening bilateral lower extremity swelling and hyperpigmentation over the past year. She initially noticed significant pruritus of lower extremities and later developed hyperpigmentation and edema. She had significant ophthalmopathy. Patient also noted thickening of a childhood scar on her right thenar eminence and a thyroidectomy scar. Patient had not used systemic or topical medications. She had used compression stockings with good effect.

Past Medical History: Graves disease

Family History: Mother with type II diabetes, died at age 48 of unknown cause

Allergies: None

hypromellose 0.25-0.3 % drops, clobetasol 0.05% ointment, fluocinolone 0.025% cream, levothyroxine 150 mcg tablet

Physical Examination

General: Well appearing woman in no acute distress
Skin: There is prominent proptosis of the globes and notable swelling of the periorbital soft tissues. On the bilateral shins, calves, and dorsal feet, there is circumferential woody induration, non-pitting edema and hyperpigmented plaques with many overlying shiny, fleshy, hyperpigmented papules and nodules throughout. On the right thenar eminence, there is a large firm nodule underlying a hyperpigmented scar. There is a hypertrophic, hyperpigmented thyroidectomy scar over the anterior neck.

Laboratory Data

- Free T4 1.32 ng/dL (normal)
- TSH 3.93 uIU/ml (elevated)
- Thyrotropin receptor antibody 36.31 IU/L (elevated)
- Thyrotropin stimulating immunoglobulin 474% baseline (elevated)
- Vitamin D 28 ng/mL (decreased)

Histopathology

Punch biopsy from the right lower leg revealed deposition of abundant myxoid material in the superficial to mid-dermis consistent with myxedema.

Treatment

- Daily compression stockings
- Clobetasol ointment to legs under plastic wrap occlusion
- Start pentoxifylline 400 mg BID, and increase to TID as tolerated after 1 week
- Schedule appointment with lymphedema specialist for lymphatic massage

CASE 20

A 27-YEAR-OLD WOMAN WITH HYPERPIGMENTATION, EDEMA, AND NODULARITY OF THE LOWER EXTREMITIES

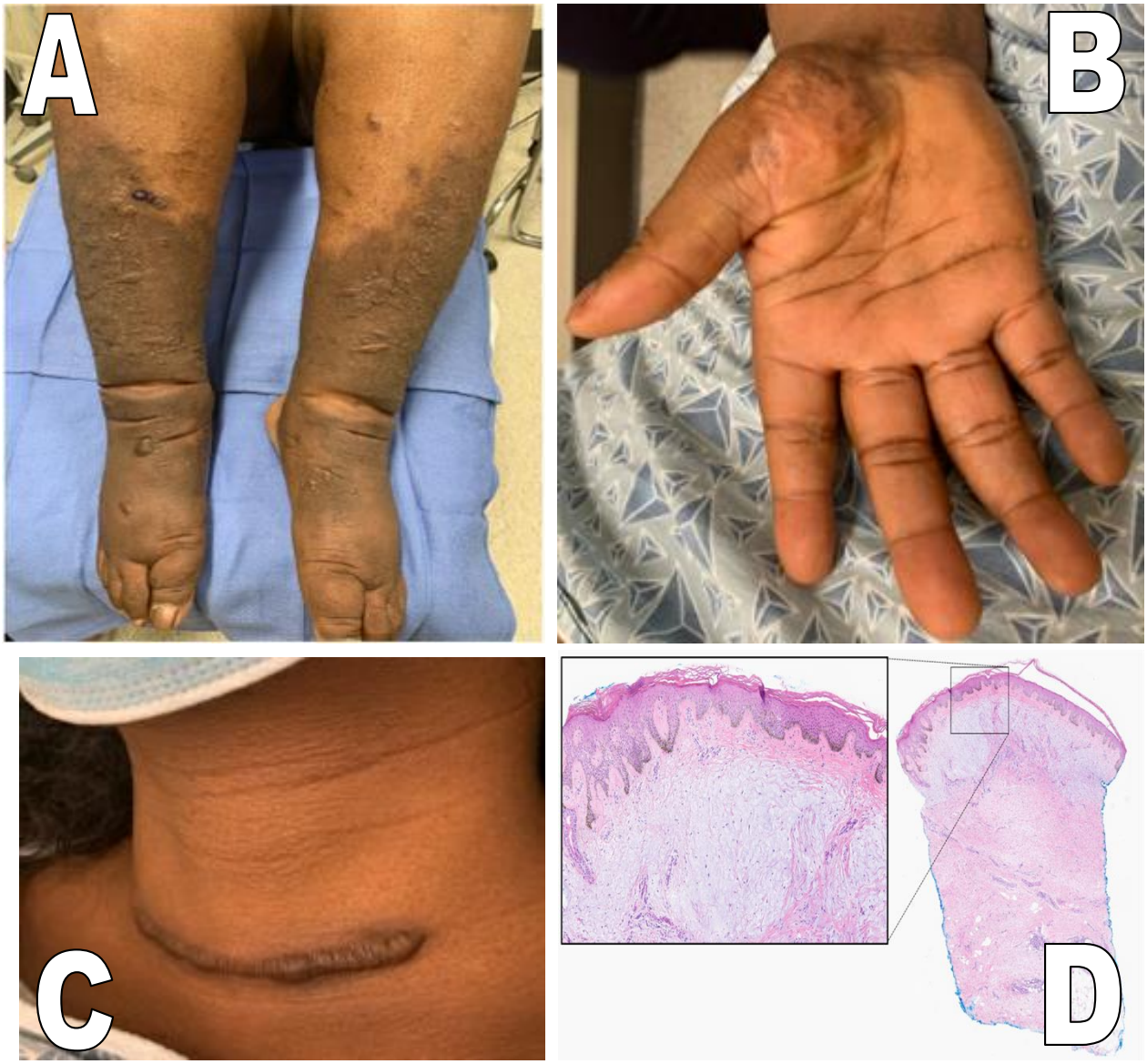

Figure: A. Bilateral lower extremities with woody induration and hyperpigmented plaques; B. and C. Hypertrophic, hyperpigmented scarring over right thenar eminence and anterior neck. D) biopsy demonstrating deposition of abundant myxoid material in the superficial to mid-dermis consistent with myxedema.

PRETIBIAL MYXEDEMA

Discussion

- Pretibial myxedema, or thyroid dermopathy, is a rare, cutaneous manifestation of autoimmune thyroid disease seen in Graves disease (GD) and, less commonly, Hashimoto thyroiditis or euthyroid patients. The prevalence of pretibial myxedema has been estimated to be 0.5%-4% in patients with Graves disease.
- Clinical findings include firm, nonpitting, *peau d'orange* edema associated with indurated plaques and nodules that can demonstrate yellow-red discoloration. These lesions are located mostly over the anterior shins but can involve the feet, thighs and upper extremities. Rare findings include hypertrichosis and hyperhidrosis of involved skin, polypoid lesions and elephantiasis-like edema.
- Clinical variants of pretibial myxedema include nodular, plaque, diffuse swelling, mixed, tumor, and elephantiasis.
- Histopathology demonstrates large amounts of mucin deposition throughout the dermis and subcutis.
- The pathophysiology of pretibial myxedema includes both cellular and humoral activation of fibroblasts that results in excess production of glycosaminoglycans, predominantly hyaluronic acid.
    - Graves ophthalmopathy shares similar pathophysiologic pathways to pretibial myxedema, with the classical finding of bilateral exophthalmos thought to result from pathologic fibroblast production of glycosaminoglycans within the periorbital dermis.
- Importantly, the myxedematous infiltrative dermopathy of autoimmune thyroid disease can manifest in susceptible individuals irrespective of whether a clinically euthyroid state is achieved by medical therapy.
- Differential diagnosis could include nephrogenic systemic fibrosis, scleroderma, scleromyxedema, tumid lupus erythematosus, lymphedema, elephantiasis, hypertrophic lichen planus or stasis dermatitis.

Teaching Points

- Almost all cases of thyroid dermopathy are associated with concomitant ophthalmopathy which is usually relatively severe and typically appears earlier than the dermopathy.
- Pathogenesis of this disease involves cellular and humoral activation of fibroblasts. In addition to pretibial myxedema, our patient had hypertrophy and thickening of prior and recent scars. There have been reported cases of pretibial myxedema appearing in prior scars suggesting that thyroid dermopathy leads to a profibrotic state.
- Diagnosis is based on clinical signs of pretibial skin lesions in association with history of Graves hyperthyroidism and ophthalmopathy. Diagnosis is often clinical; however, skin biopsy can be performed for confirmation.
- Control of thyrotoxicosis typically has no effect on dermopathy.
- Providers may consider topical corticosteroid therapy applied under occlusive dressing, intralesional corticosteroids, and/or pentoxifylline for symptomatic cases.
- For patients with advanced forms of disease, such as the elephantiasis variant and thyroid acropachy, local compressive therapy may have added benefit.
- For severe forms, systemic immunomodulatory therapy may be necessary including oral corticosteroids, IVIG, octreotide, rituximab, or plasmapheresis.

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