NEW ENGLAND DERMATOLOGICAL SOCIETY
CLINICAL MEETING
Saturday, April 6, 2024
UMass Chan Medical School Department of Dermatology
April 6, 2023

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.

Sincerely,

Gabriela Cobos, MD
Secretary
New England Dermatological Society
www.nederm.org
FUTURE MEETINGS OF THE
NEW ENGLAND DERMATOLOGICAL SOCIETY

October 5, 2024 – Clinical Meeting
Hosted by:
Yale School of Medicine
New Haven, CT

December 7, 2024 – Clinical Meeting
Hosted by:
Boston University Chobanian & Avedisian School of Medicine
Boston, MA
New England Dermatological Society (NEDS) 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 trainee who wrote up the case then presents the case at the American Academy of Dermatology (AAD) in the gross and microscopic session they 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 trainee who wrote up the winning case and who is recommended for this award by the physician overseeing the case. The award recipient is awarded a $500 Amazon gift card towards the purchase of medical textbooks.

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

Book Award
NEDS will award a $500 gift card towards the purchase of a medical textbook to any trainee at a member institution who satisfies the following requirements:

1. The trainee is a first author of a report based on a case presented at a NEDS meeting.

2. The report is accepted for publication by a peer-reviewed journal within two years of the NEDS meeting and contains language indicating that the “this case was presented at a meeting of the New England Dermatological Society held at (institution) on (date).”

3. The trainee supplies the NEDS Administrator with a copy of the final journal acceptance letter and a receipt for their purchased medical textbook. If approved by NEDS, the trainee is awarded a gift card in the amount of $500 towards the purchase of their medical textbook.
IMPORTANT

Conference Evaluation and CME Information

Meeting attendees will receive an email from NEDS on Saturday, April 6, 2024 with a link to the Survey Monkey® online meeting evaluation for this activity. This message will be sent to your registration email address.

If you do not receive this email, alert the NEDS Administrator.

The deadline to complete the evaluation is Monday April 29, 2024 at 7:00 AM EST.

Those who meet the evaluation deadline will receive an email from kelli.landry@lifespan.org by Friday, May 17, 2024 regarding delivery of your CME certificate.

This meeting is eligible for up to 4.25 AMA PRA Category 1 Credits™. Attendees should claim only the credit commensurate with the extent of their participation in the activity.

For further questions, contact Gayle Sommer / NEDS Administrator
781-434-7731  NEDS@mms.org.
**April 6, 2024**  
**NEDS Clinical Meeting Hosted by UMass Chan School of Medicine**  
**Department of Dermatology**  
**Agenda**

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<td>7:45 - 9:15 am</td>
<td>Registration and <strong>Patient Viewing</strong> (iCELS - UMass Chan Medical School)</td>
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<td>9:15 - 10:30 am*</td>
<td>Breakfast and Exhibits (Beechwood Hotel)</td>
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<td>10:15 - 10:30 am*</td>
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| 10:30 - 10:35 am | **Introduction / Welcome**  
John E. Harris, MD, PhD and Dori, Goldberg, MD                                          |
| 10:35 - 10:55 am | **Multi-Disciplinary HS Care and Optimizing Outcomes in HS**  
Jessica St John, MD, MPH, MBA, Sarah Whitley, MD, PhD                                     |
| 10:55 - 11:25 am | **Case Discussion 1-7**  
Moderators:  
Rita Khodosh, MD, PhD, Sarah Whitley, MD, PhD, Zoe Brown-Joel, MD                      |
| 11:25 - 11:40 am | **Unraveling the Mystery Box: Useful Tools in the Diagnosis of CTCL**  
Ryan Svoboda, MD, MS                                                                     |
| 11:40 am - 12:00 pm* | Coffee Break/Exhibits Open                                                               |
| 12:00 - 12:30 pm | **Case Discussion 8-15**  
Moderators:  
Rita Khodosh, MD, PhD, Sarah Whitley, MD, PhD, Zoe Brown-Joel, MD                      |
| 12:30 - 12:45 pm | **Emerging Therapies for Epidermolysis Bullosa**  
Diana B. Reusch, MD                                                                        |
| 12:45 - 1:20 pm | **Case Discussion 16-22**  
Moderators:  
Rita Khodosh, MD, PhD, Sarah Whitley, MD, PHD, Zoe Brown-Joel, MD                       |
| 1:20 - 1:35 pm | **Final Comments**  
John E. Harris, MD, PhD and Dori, Goldberg, MD                                          |
| 1:35 pm | Meeting adjourns, boxed lunches provided                                                  |

*ineligible for CME credits*
Welcome to the New England Dermatological Society Meeting at the University of Massachusetts Chan Medical School.

First and foremost, we thank our greatest teachers, our patients. We are grateful for the privilege to care for each and every individual and for their willingness to participate in today’s meeting.

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 thank our outstanding moderators Dr. Jessica St. John, Dr. Rita Khodosh, and Dr. Zoe Brown-Joel. We greatly appreciate their commitment to educational and academic excellence.

Next, we thank our guest speakers Dr. Diana Reusch, Dr. Jessica St. John, Dr. Ryan Svoboda, and Dr. Sarah Whitley for sharing their exceptional research and clinical expertise.

We also thank the faculty who graciously and expertly care for the patients discussed today. They include Dr. Diana Reusch, Dr. Fnu Nutan, Dr. Jessica St. John, Dr. Karen Wiss, Dr. Leah Belazarian, Dr. Mark Scharf, Dr. Mehdi Rashighi, Dr. Nikki Levin, Dr. Ryan Svoboda, and Dr. Sarah Whitley.

To our resident physicians: thank you for reading the countless emails and text messages. Thank you for checking in and going above and beyond what is required of you. We thank Dr. Elana Putterman, Dr. Sarah Servattalab, Dr. Colleen Gabel, Dr. Lindsay McCormack, Dr. Maggi Ahmed, Dr. Nicholas Leonard, Dr. Holly Neale, Dr. Kelly Flanagan, Dr. Shauna Rice, and Dr. Sina Forotangazi.

We next thank our dermatopathologists, who brought their exemplary diagnostic skills, life-long clinical lessons, and passion to this meeting. They are Dr. Patrick O’Donnell, Dr. Soheil Dadras, Dr. Zoe Brown-Joel, and Dr. Zendee Elaba.

We would like to thank our administrative assistants Esmeralda Valois, Marcia Boulanger, and Patricia Begin for their extraordinary coordination that made this meeting happen. We also thank Gayle Sommer for her experienced guidance throughout this journey.

We thank the medical students who dedicated their time to preparing excellent case write-ups. They include Alice Tan, Allison Holt, Amina Tariq, Anthony Camargo, Beatriz Fernandes, Carolyn Foley, Chidobe Umeasor, Chris Mahir, Christine Li, Elaine Flynn, Emily Herringshaw, Emily Meara, Erica Huang, Grace Hanrahan, Haley Neff, Jane Chuprin, Jenny Chung, Jessica Orofino, Khashayar Afshari, Michael Frisoli, Morgan Groover, Nazgol Haddadi, Nicole Loranger, Noah Miranda, Priscilla Romano, Robert Li, Ryan Chen, Shiv Malhotra, Stephanie Choi, Tinyan Omere, Toireasa Rafferty-Millett, Vincent Azzolino, and Yuying Zhan. The future is bright.

We thank the casebook editors Dr. Bella Plumptre, Dr. Karen Wiss, Dr. Leah Belazarian, and Dr. Nikki Levin. Your attention to detail is so appreciated. A special thank you to Dr. Bella Plumptre for her late night copy edits and for recognizing that every capital and period is important.

We thank our gracious program director Dr. Patrick Mulvaney for his constant support.

We are grateful to our visionary chair Dr. John Harris for his commitment to excellence.

Finally, we thank our fearless and tireless lead planner, Dr. Dori Goldberg, for her diligent work and leadership. We couldn’t do this without you.

Sincerely,
Dr. Mary Awad
Dr. Heather Gochnauer
Chief Resident Planners
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CASE 1
A 31-YEAR-OLD WOMAN WITH HIDRADENITIS SUPPURATIVA, PSORIASIS, NEUTROPHILIC PUSTULOSIS, UVEITIS, AND ARTHRITIS

Patient
BG is a 31-year-old woman.

Presenters
Antony M. Camargo, MSIII
Yuying Zhang, MSII
Nicholas Leonard, MD
Jessica St. John, MD, MPH, MBA
Karen Wiss, MD

History
A 31-year-old woman who has been seen in UMass dermatology clinic for the past 15 years presented for evaluation. She had a history of hidradenitis suppurativa (HS), Hurley stage III, diagnosed at age 6. Her dermatologic history also includes psoriasis, particularly of the scalp and ears, neutrophilic pustulosis, and pyoderma gangrenosum. During her HS flares, she often experiences symptoms of fatigue, malaise, uveitis, and arthritis with inflammatory pustules on the face, trunk, and extremities. She was evaluated in 2011 at the National Institutes of Health (NIH) and no genetic abnormality was identified. She has tried and not improved on infliximab, adalimumab, ustekinumab, secukinumab, dapsone, and methotrexate. Her flares respond well to oral prednisone. Upon presentation, she is partially controlled on anakinra and cyclosporine, but flares with pustules and psoriasis when the cyclosporine is tapered. She also has required short courses of doxycycline for pustular outbreaks on the face.

Past Medical History: Psoriasis, arthritis, hidradenitis suppurativa, pyoderma gangrenosum, and ulcerative colitis (asymptomatic)

Family History: Sister (42) with sarcoidosis and sister (40) with congenital hearing loss. Brother with HS.

Allergies: Levofloxacin

Medications: Anakinra, cyclosporine, doxycycline

Physical Examination
Axillae with linear, well-healed surgical scars. Scattered, pink, inflammatory papules and pustules on the trunk and extremities. Thick, adherent plaques with silverly scale over most of the scalp. Bilateral inguinal folds and medial thighs with interconnected sinus tracts with scarring.

Laboratory Data
- CBC, CMP, lipid panel WNL other than reduced MCV consistent with thalassemia trait
- ANA, ANCA screen were negative
- ESR and CRP levels were WNL
- TB, Hepatitis panel, HIV tests negative
- Hypercoagulable tests negative
- Anti-Saccharomyces cerevisiae (ASCA) antibody elevated (indicator of IBD)
- Colonoscopy without evidence of IBD (2013)
- Genetic testing at NIH in 2011 unrevealing

Histopathology
Biopsies of pustules on left upper back and left dorsal hand (Figure 1B) performed in March 2023 revealed suppurative neutrophilic folliculitis.

Treatment
- Laser hair removal in bilateral axillae 2012
- Surgical deroofing of bilateral axillae 2023
- Cyclosporine, doxycycline, and anakinra were discontinued
- Upadacitinib 15 mg PO daily after an induction dose of 45 mg PO daily for 8 weeks
- After 2 weeks on upadacitinib, symptoms of fatigue, malaise, uveitis, and arthritis resolved. Her skin has remained largely clear for the past 8 months, except for a few small pustules and papulonodules in the bilateral axillae and a small psoriasis plaque in the left groin.
CASE 1
A 31-YEAR-OLD WOMAN WITH HIDRADENITIS SUPPURATIVA, PSORIASIS, NEUTROPHILIC PUSTULOSIS, UVEITIS, AND ARTHRITIS

Figure 1: Photos prior to treatment with upadacitinib. (A) Inflammatory papules and pustules scattered on the chest; (B) left dorsal hand with inflammatory pustule (biopsied); (C) and (D) left hip, buttocks, and posterior thighs with inflammatory papules and papulonodules with surrounding erythema; (E) uveitis of right eye; (F) pityriasis amiantacea of the left vertex scalp.

Figure 2: Bilateral axillae (G) at time of surgical deroofing; (H) 10 days after deroofing; (I) six months after deroofing. Note linear scars with surrounding inflammatory papules.
PsAPASH SYNDROME: PSORIATIC ARTHRITIS, PYODERMA GANGRENOsum, ACNE, SUPPURATIVE HIDRADENITIS

Discussion

- Hidradenitis suppurativa (HS) is a chronic, inflammatory condition that primarily affects intertriginous areas (axillae, groin, inframammary skin, gluteal cleft) and is characterized by recurrent, painful, malodorous nodules and abscesses that can lead to scarring, sinus tract formation, and fistulae.
- The pathophysiology of HS is complicated and not well understood, though pro-inflammatory cytokines such as tumor necrosis factor (TNF) α, interferons (IFN) α/β/γ, interleukins (IL) 1, 6, and 17 are often elevated in HS skin and blood. The JAK/STAT signaling pathways are also involved.
- Treatment for HS remains limited and inadequate. Treatment regimens often include a combination of several of the following: topical and oral antibiotics, anti-androgen therapy (e.g., spironolactone), retinoids, systemic immunomodulators (e.g., methotrexate, dapsone), and biologics. To date, only TNF α inhibitors (e.g., adalimumab) and more recently secukinumab, an IL-17 inhibitor, are approved by the FDA for HS treatment. JAK inhibitors are emerging as an effective treatment modality for patients with HS.
- Upadacitinib is a selective JAK1 inhibitor, which interferes with the JAK-STAT signaling pathway, thus suppressing transduction of IL-6, IL-23, IL-21, and IL-22 cytokine signals. A recent study demonstrated a positive clinical response in patients treated with upadacitinib with 75% of patients experiencing at least a 50% reduction in lesion count and pain in just 4 weeks of treatment.
- HS is also associated with PASH-spectrum autoinflammatory syndromes. PASH (pyoderma gangrenosum (PG), acne, and suppurative hidradenitis) is an autosomal dominant autoinflammatory syndrome due to mutations in PSTPIP1 or NCSTN. Some have proposed that PASH includes a spectrum of disorders with a common pathogenic mechanism involving IL-1-driven recurrent episodes of neutrophil-predominated sterile inflammation. These syndromes include PAPA (PG, acne, pyogenic arthritis), PAPASH (PG, acne, pyogenic arthritis, and suppurative hidradenitis), and PsAPASH (psoriatic arthritis, PG, acne, and suppurative hidradenitis), among others. Aside from PSTPIP1 and NCSTN, no definitive pathogenic mutations have been identified in these syndromes. These disorders have been reported to improve with IL-1, TNF α, and IL-17 blockade.

Teaching Points

- This patient’s HS flares often presented with malaise, fatigue, uveitis, arthritis, and outbreaks of neutrophilic pustules throughout the body, often on the face and nose, supporting a diagnosis of PsAPASH. Genetic mutations associated with PsAPASH are still unknown and genetic testing is pending for this patient.
- Surgical excision or deroofing for HS can be extremely beneficial, even life-changing, by removing existing disease that will never resolve despite medical treatment optimization. This patient’s deroofing sites healed quicky with linear scars while on secukinumab.
- JAK inhibitors are emerging as effective treatments for HS patients, and may be particularly effective in patients who also have a history of inflammatory bowel disease and/or psoriasis as in this case.

References:
CASE 2
A 37-YEAR-OLD MAN WITH ERYTHEMA, INDURATION, NODULES, AND DRAINING ABSCESSES OF BILATERAL BUTTOCKS

Patient
CG is a 37-year-old male.

Presenters
Toireasa Rafferty-Millett, MSIII
Erica Huang, MSII
Colleen Gabel, MD
Sarah Whitley, MD, PhD, FAAD

History
A 37-year-old wheelchair-bound male with PMH of thromboembolic stroke with residual weakness, chronic pain with opioid dependence, and tobacco use presented with a ~20 year history of progressively worsening abscesses on the bilateral buttocks and posterior thighs. He complained of copious bloody drainage and severe pain. He was diagnosed with hidradenitis suppurativa (HS) two years earlier, and prior treatments included adalimumab, oral antibiotics, topical antimicrobials, and numerous I&Ds. Treatments at initial presentation included secukinumab 300 mg q2wks, acitretin 17.5 mg daily, and topical antimicrobials.

Two years after starting adalimumab, the patient experienced a leftICA stroke propagated by an aortic arch thrombus. Neurology attributed the stroke to adalimumab and it was discontinued. He was subsequently started on apixaban.

Acitretin was stopped and the patient was continued on secukinumab 300 mg q2wks, with addition of methotrexate 10 mg weekly and folic acid 1 mg daily until canakinumab was approved. Since starting canakinumab, his HS considerably improved, with significant reduction in induration and erythema. Three months into treatment, he underwent left buttock HS excision with Plastic and Reconstructive Surgery, left to heal by secondary intention, with significant clinical improvement. His surgical course was complicated by pain.

Past Medical History: HS Hurley stage III, DVT, thromboembolic LICA stroke with residual RUE and RLE weakness and spasticity, on apixaban, anemia (IDA vs. AOCD).

Family History: Mother and maternal grandfather with HS, maternal grandfather and great-grandfather with history of stroke.

Allergies: None

Medications at initial presentation: Acitretin 17.5 mg, secukinumab 300 mg q2wks, clindamycin 1% gel, chlorhexidine 4% liquid, apixaban, amlodipine, duloxetine, gabapentin 300 mg TID, baclofen 20 mg QID, acetaminophen 650 mg q6h, docusate sodium, senna, polyethylene glycol, omeprazole, scopolamine transdermal film, tizanidine.

Physical Examination
Fluctuant plaques and woody induration affecting the entire right buttock (23 cm x 23 cm x 0.5 cm involvement), left buttock (15 cm x 17 cm x 0.5 cm involvement), and the posterior right thigh, some in a retiform configuration. Plaques are studded with firm nodules +/- ulceration, many draining blood and purulent material. On initial presentation, an indwelling penrose drain was noted on R buttock. Double headed comedones present in bilateral axillae but no other skin lesions in groin, chest, or neck.

Laboratory Data
• Hemoglobin 9.9 g/dL (low); hematocrit 35.1% (low); CMP within normal limits

Histopathology
Excision from left buttock revealed skin with complex, benign, keratinizing, stratified squamous epithelium-lined cystic structure with rupture, granulation tissue, and acute and chronic inflammation in the fibroadipose tissue of dermis and subcutaneous soft tissue consistent with hidradenitis suppurativa.

Treatment
• Current: canakinumab 150mg subcutaneous injection every 28 days
• Co-management with plastic surgery for WLE of HS on bilateral buttocks in a staged fashion
• Referred to hematology/oncology & pain medicine
CASE 2
A 37-YEAR-OLD MAN WITH ERYTHEMA, INDURATION, NODULES, AND DRAINING ABSCESSES OF BILATERAL BUTTOCKS

Figure: (A) Initial presentation. (B) Reduction in induration, nodularity, and drainage two weeks after the first canakinumab 150 mg injection. (C) Significantly reduced induration, nodularity, and drainage after the third treatment with canakinumab 150 mg.
HIDRADENITIS SUPPURATIVA

Discussion

- In HS, immune dysregulation leads to excess proinflammatory cytokines, including IL-1β, IL-17, and TNF-α.
- The risk of adverse cardiovascular outcomes (MI, ischemic stroke, and CV-associated death) is significantly increased in patients with HS, independent of age, sex, smoking, and medications.
- TNF alpha inhibitors (TNFi), used for HS treatment, have been associated with increased risk of thromboembolism (TE). This risk may be attributable to TE-associated antibody development while on TNFi (HR 7.6; 95% CI 0.9-15.3, p=0.025). These include lupus anticoagulant (etanercept), anti-dsDNA and anticardiolipin (infliximab), and anti-adalimumab (adalimumab). In 8 patients with adalimumab-induced TE, 4 had anti-adalimumab Abs. TE incidence was 26.9/1,000 person-years for patients with anti-adalimumab Ab and 8.4/1,000 person-years for patients without Abs (HR 3.8; 95% CI 0.9-15.3, p=0.064).
- JAK inhibitors (JAKi), used off-label for HS treatment, are associated with increased risk for major cardiovascular events (MACE) and stroke in those with atherosclerotic cardiovascular disease (ASCVD), and increased risk of PE and all-cause mortality in those with >1 CV risk factor. In a study of patients with CAD, HR of VTE was 1.34 in tofacitinib-treated patients compared with TNFi-treated patients.
- Unlike TNFi or JAKi, an association between secukinumab and thromboembolic events has not been reported.
- The decision was made to avoid TNFi and JAKi in our patient out due to risk of thromboembolism.
- Canakinumab is a fast-acting, off-label therapy for HS, which can be considered for TNFi-refractory HS or those with prior MACE or history of VTE. Canakinumab is an IgGk monoclonal antibody that neutralizes IL-1β signaling and has been reported to be effective in severe cases of HS non responsive to traditional therapies.
  - Patients with a history of MI who were treated with canakinumab 150 mg had significantly lower rates of nonfatal MI, nonfatal stroke, and CV-death compared to placebo (CANTOS trial).
  - It is currently administered as a monthly injection without a loading dose. However, it does not have spring-loaded syringe for easy self injection, and must be reconstituted. It is advised that patients have 1-2 injections in a healthcare setting before continuing with family-assisted injections at home.

Teaching Points

- Thrombotic events have been observed in about 4.5% of patients treated with TNFi, possibly attributable to antibody production such as anti-dsDNA, antiphospholipid, and anti-β2-glycoprotein antibodies.
- Canakinumab is fast-acting, effective, off-label therapy for patients with severe treatment-refractory HS, especially for those with a history of MACE and/or ASCVD for whom TNFi and JAKi are contraindicated. Canakinumab may improve CV outcomes for all HS patients given their baseline increased risk of CV morbidity.

References:

CASE 3
A 58-YEAR-OLD MAN WITH WORSENING SYSTEMIC SYMPTOMS AND PURPURIC RASH

Patient

FG is a 58-year-old man.

Presenters

Chidobe Umeasor, MSII
Morgan Groover, MSIV
Nicholas Leonard, MD
Maggi Ahmed, MD
Nutan Fnu, MD

History

A 58-year-old man with no significant past medical history presented to the emergency room after experiencing worsening shortness of breath, cough with bloody sputum, fever, headaches, and a new rash for the past 3 days. Twenty months prior to presentation, he developed asthma-like symptoms which resulted in several hospital admissions for acute hypoxemic respiratory failure. Each exacerbation improved modestly with short prednisone tapers, but respiratory symptoms persisted between admissions, eventually leading to a diagnosis of occupational asthma. Ten days prior to presentation, he was started on dupilumab for his asthma.

Past Medical History: Noncontributory
Family History: Noncontributory
Allergies: None
Medications: Budesonide/formoterol, albuterol, ipratropium, montelukast, amlodipine, losartan, pantoprazole, prednisone 50 mg daily

Physical Examination

General: Well appearing male mildly short of breath at rest
Skin: Numerous pink to violaceous non-blanchable papules and plaques were distributed on the upper and mid back. A single erythematous, edematous plaque was noted on the left lower back. Nikolsky and Asboe-Hansen signs were negative. There was no mucous membrane involvement.

Laboratory Data

- Leukocyte count 25,200/uL (elevated)
- Eosinophils 13.4% (elevated)
- Eosinophil count 3,400/uL (elevated)
- CRP 25.1 mg/L (elevated)
- Rheumatoid Factor <14 IU/mL (normal)
- P-ANCA Titer 1:640 (elevated)
- Myeloperoxidase antibody 5.4 (elevated)

Histopathology

A punch biopsy from the left lower back revealed leukocytoclastic vasculitis with abundant eosinophils.

Treatment

- Discontinuation of dupilumab
- Methylprednisolone 48 mg PO daily, tapered over 19 days
- Budesonide-formoterol 160-4.5 mcg inhaler 2 puffs BID
- Albuterol 90 mcg inhaler q 2 hours PRN
- Benzonatate 100 mg PO TID PRN
- Dextromethorphan-guaifenesin 20-200 mg/10 mL syrup, 5 mL PO q 6 h PRN
- Transitioned to mepolizumab 100 mg monthly in the outpatient setting upon discharge.
CASE 3
A 58-YEAR-OLD MAN WITH WORSENING SYSTEMIC SYMPTOMS AND PURPURIC RASH

Figure: (A) Lung CT showing bilateral infiltrates and bronchial wall thickening, with parabronchial opacities mostly in the left lower lobe. (B) Erythematous to violaceous plaques on the upper and mid back. (C) Punch biopsy revealing leukocytoclastic vasculitis with eosinophils.
Eosinophilic Granulomatosis with Polyangiitis Exacerbated by Dupilumab

Discussion

- Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg Strauss Syndrome, is a necrotizing small vessel vasculitis characterized by abundant eosinophils in areas of granulomatous inflammation.
- EGPA is a very rare disease, with an incidence 0.5 to 2.7 cases per million per year.
- Histopathologic findings include leukocytoclasis with necrotizing, extravascular granulomas containing eosinophils. Fibrin deposits may be seen in blood vessel walls.
- Vasculitis may present on the skin as palpable purpura, hemorrhagic bullae, or erythematous papules.
- The pathophysiology is poorly understood, but it is believed to be secondary to ANCA-dependent activation of neutrophils resulting in vasculitis. In addition, there may be an upregulated immune response where IL-5 released by Th2 lymphocytes induces overactivity of peripheral eosinophils.
- EGPA may present in 3 clinical phases. The initial prodrome phase is characterized by rhinitis, sinusitis, and adult-onset asthma. In the second phase, there is peripheral eosinophilia with eosinophilic infiltrate in various organs. The third is the vasculitic phase, with neurological symptoms, systemic vasculitis, purpura, and other symptoms of multisystem damage. The initiation of dupilumab prior to symptom progression in our patient raises the question of whether dupilumab precipitated or hastened the initiation of the vasculitis phase. There have been several cases in the literature of dupilumab exacerbating or “unmasking” EGPA, as well as 6 cases of EGPA reported as adverse events in dupilumab clinical trials for asthma and chronic rhinosinusitis with nasal polyps.
- The pathogenesis of dupilumab unmasking EGPA is unknown, but it is postulated that while the drug prevents eosinophil migration and activation in the airways, it may be unable to suppress IL-5-induced peripheral eosinophil activity.

Teaching Points

- Dermatologists may play a role in diagnosing EGPA, particularly in its vasculitis phase where cutaneous lesions appear.
- To our knowledge, there have been no cases of EGPA reported of patients receiving dupilumab primarily for atopic dermatitis. Dermatologists should be aware of the potential for dupilumab to unmask EGPA.

References:

**CASE 4**

**A 44-YEAR-OLD MAN WITH LIVEDO RACEMOSA AND STROKE LIKE EPISODES**

**Patient**

TK is a 44-year-old man.

**Presenters**

Nazgol Haddadi, MD, MPH  
Mary Awad, MD  
Seyedeh Nasim Cheraghi, MD  
Mehdi Rashighi, MD

**History**

A 44-year-old male who was recently diagnosed with complex migraines was hospitalized with multiple neurologic complaints, including headaches, tinnitus, blurred vision, fluctuating numbness and speech disturbances, unsteady gait, cognitive impairment, and a new rash. The initial work-up confirmed encephalopathy, sensorineural hearing loss, and retinal hemorrhage, with MRI scans indicating multiple scattered small infarcts throughout the brain. The skin lesions were asymptomatic and developed on the abdomen and lower extremities a few days after admission, with no significant progression during the hospital course. He denied any prior history of a similar rash, recent travel, or sick contacts.

**Past Medical History:** Migraine headaches  
**Family History:** Noncontributory  
**Allergies:** None  
**Medications:** Aspirin, atorvastatin, sumatriptan

**Physical Examination**

The patient has diffuse, mildly erythematous, discontinuous, semi-recticular, blanchable patches in an irregular pattern observed across the trunk, hips, thighs, and posterior calves, representing livedo racemosa.

**Laboratory Data**

- Negative tests: Blood: CCP (<16 units), DNA (DS) AB (<1 IU/mL), Sm AB (<1), RNP AB (<1), cryoglobulin, C3C (162 mg/dL), C4C (45 mg/dL), SSA/B (<1), ANCA, ANA, APLS panel (Beta2-glycoprotein IgG/A/M, phosphatidylserine IgG/M), cardiolipin AB (IgG/A/M, antithrombin III (103%), protein S (77%); CSF: autoimmune neurologic AB (i.e., Myelin, GAD65, NMDAR1, CASPR2), West Nile AB IgG (<1.30) and IgM (<0.9), infectious meningitis panel, Babesia microti DNA, Ehrlichia, or Lyme (<0.9) were not detected.
  - Borderline tests: CSF: acetylcholine receptor ganglionic (alpha 3) Ab 83 pmol/L (borderline 55-160 pmol/L, CSF) and phosphatidylserine IgA 28 U/mL (<20 U/mL)
  - Brain MRI with and without contrast showed punctate focus of restricted diffusion in the corpus callosum (snowball lesions), basal ganglia, and frontal lobes. T2 hyperintensity of the left internal capsule and right cerebellar hemisphere was noted. Cerebellar leptomeningeal enhancement was also seen.
  - Intervential radiology angiography showed no evidence of vasculitis or large vessel occlusion.
  - Audiometry showed mild to moderate sensorineural hearing loss on the right side.
  - Fundoscopy exam elucidated inferior retinal vasculitis in the left eye.

**Histopathology**

Punch biopsies from non-lesional areas on the flank and hip revealed mild perivascular lymphocytic infiltrate, superficial vascular ectasia, and vascular congestion, with no signs of thrombotic vaso-occlusive processes or vasculitis. Periodic Acid-Schiff and Leder staining did not reveal any specific findings.

**Treatment**

- Methylprednisolone 1 g IV injection for 5 days  
- One course of oral prednisone treatment with slow tapering and cyclophosphamide 900 mg via IV infusion every two weeks for a total of 6 cycles  
- Mycophenolate mofetil 1 g BID  
- Aspirin 81 mg daily, atorvastatin 80 mg daily, meclizine 25 mg TID PRN, ondansetron 8 mg TID PRN
CASE 4
A 44-YEAR-OLD MAN WITH LIVEDO RACEMOSA AND STROKE LIKE EPISODES

Figure: Livedo racemosa on abdomen (A) and flank (B) characterized by non-continuous, blanchable net-like pattern of erythema. (C) and (D): Punch biopsies from the left flank displayed vascular congestion and focal vascular ectasia with a mild perivascular lymphocytic infiltrate (green arrowhead). No vasculitis or thrombi are seen. MRI shows multiple hyperintense white matter lesions on FLAIR sequence in axial (blue arrowhead) (E) and sagittal views (F), indicative of "snowball lesions" within the corpus callosum (red arrowhead).
Susac’s Syndrome

Discussion

- Susac’s syndrome is a rare autoimmune endotheliopathy of the microvasculature characterized by the triad of encephalopathy, branch retinal artery occlusions (BRAO), and hearing loss (HL).
- Typical brain MRI findings essential for the diagnosis include multiple T2 hyperintensities in the white matter, always involving the corpus callosum.
- Cytotoxic CD8+ T-lymphocytes and auto-endothelial cell antibodies (AECAs) are hypothesized to play a key role in the pathogenesis of these symptoms.
- Skin involvement, such as livedo racemosa and livedo reticularis, occurs in fewer than 5% of patients. Livedo, especially livedo racemosa, results from irregular focal and persistent impairment of blood flow.
- Skin biopsies from erythematous areas may be normal, whereas a biopsy specimen from non-involved skin between the livedo nets may show a thrombus in arterioles, complement component deposition, endothelial cell swelling, dermal venous congestion, and perivascular inflammation.
- There are no specific serological markers for this syndrome.
- Important differential diagnoses in an encephalopathic patient with livedo racemosa include:
  - Sneddon’s syndrome: This is characterized by hypercoagulability and vascular manifestations, including subendothelial smooth muscle cell accumulation, without typically affecting the cochlea, CSF protein, or cell count, and lacking MRI lesions in the center or roof of the corpus callosum, often presenting with central retinal artery occlusion (CRAO) instead of BRAO.
  - Antiphospholipid antibody syndrome: This is associated with a hypercoagulable state and serum antiphospholipid antibodies.
  - Neuropsychiatric systemic lupus erythematosus: This is associated with high titers of serum autoantibodies and reduced complement levels.
  - Polyarteritis nodosa: This is a systemic necrotizing vasculitis with widespread organ involvement, including kidneys.
- Treatment options include corticosteroids, intravenous immunoglobulin (IVIG), mycophenolate mofetil and/or rituximab for breakthrough disease followed by cyclophosphamide, and aspirin and atorvastatin for secondary stroke prevention.

Teaching Points

- Susac’s syndrome diagnosis relies on characteristic clinical findings of brain, retinal, and vestibulocochlear involvement. However, livedo should be considered a potential manifestation of this syndrome; therefore, careful skin examination is important.
- Susac’s syndrome is an important diagnosis to consider in a patient with newly onset neurologic disease and livedo racemose or reticularis, along with better known conditions such as Sneddon’s syndrome and SLE.
- Multiple skin punch biopsies should be performed to increase the diagnostic yield, including the peripheral erythematous and central pale areas.
- Treatment is empirical and relies on prompt and sustained aggressive immunosuppression.

References:

CASE 5
A 65-YEAR-OLD MAN WITH CHRONIC NEUTROPENIA, THROMBOCYTOPENIA, AND CHRONIC VIOLACEOUS RASH

Patient
DA is a 65-year-old male.

Presenters
Vincent Azzolino, MSIII, MD/PhD candidate
Grace Hanrahan, MSII
Colleen Gabel, MD
Jessica St. John, MD, MPH, MBA

History
A 65-year-old man with a history of testicular cancer (in remission, treated 40 years prior), as well as chronic neutropenia and thrombocytopenia of unknown origin, presented with a ten year history of violaceous papules on the trunk and extremities. The patient denied pain, pruritus, or other associated symptoms. A biopsy five years prior was read as reactive angioendotheliomatosis with intravascular histiocytosis. On presentation, he noted his rash was spreading to upper thighs and a repeat punch biopsy was performed, which confirmed the diagnosis. Work-up for his neutropenia and thrombocytopenia has included a bone marrow biopsy and next generation gene sequencing, which were not indicative of a hematologic abnormality.

Past Medical History: Testicular cancer (treated 40 years prior), chronic neutropenia, thrombocytopenia (unknown origin), hyperglycemia, primary hypothyroidism, essential hypertension, depression, and mild renal insufficiency.

Family History:  
- Father (deceased): Prostate cancer, bladder cancer, diabetes.  
- Brother (living): Leukemia

Allergies: Haloperidol and cefuroxime

Medications: Levothyroxine, losartan, sertraline

Physical Examination
Many violaceous papules coalescing into plaques in a reticular pattern on the chest, upper abdomen, and upper arms. On the bilateral proximal legs were violaceous, reticular patches, most pronounced over medial proximal thighs.

Laboratory Data
- CBC (10³/µL): WBC: 2.9, neutrophils: 1.22, platelets: 102
- CMP: BUN: 26 (elevated), Cr 1.13
- Viral studies: EBV, HIV, CMV, hepatitis panel all negative
- Bone marrow biopsy (2020): notable for megakaryocyte atypia not diagnostic of myelodysplastic syndrome (MDS). Negative next generation sequencing for MDS.
- Lipid Panel: HDL: 24 mg/dL (decreased), Triglycerides 450 mg/DL (elevated)
- A1C: 6.4% (elevated)

Additional workup, which was unremarkable included: ANA, antiphospholipid antibody, cardiolipin antibodies, prothrombin, Factor V Leiden, protein C and protein S activity, antithrombin III, homocysteine, and factor VIII activity, TSH, protein electrophoresis, K/L light chains, immunofixation, LDH, PSA, alpha fetoprotein, CRP, and ESR.

Histopathology
A punch biopsy of a patch of livedoid erythema on the left medial thigh was obtained which demonstrated a proliferation of small, superficial and focally deep dermal vessels with intravascular proliferation of histiocytes, scattered perivascular T-cells, and few mast cells. Intravascular histiocytosis was confirmed with the presence of CD68 and CD163-staining histiocytes within vessels highlighted by CD31 and ERG, and a D240 highlighting rare lymphatic vessels without histiocytosis. Staining was negative for fungal elements. These features were consistent with prior biopsy, suggestive of reactive angioendotheliomatosis with intravascular histiocytosis.
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Treatment

- Oral β-blocker (metoprolol 50 mg daily) was initiated, which resulted in the lightening and decreased density of the violaceous papules on the chest and violaceous patches on the thighs after only 4 months of treatment.
- He continues to follow with his hematologist for monitoring of thrombocytopenia and neutropenia of unknown origin (10-year history).

Figure: (A) and (B): Reticular, purpuric patches consistent with livedo reticularis on the bilateral thighs before (A) and after (B) treatment with 4 months of oral metoprolol. (C) and (D): Violaceous papules coalescing into plaques on the chest and upper abdomen before (C) and after (D) treatment with oral metoprolol. (E) Punch biopsies from the chest and right thigh displayed a primarily superficial dermal vascular proliferation with bland endothelial cells and intravascular proliferation of histiocytes. (F) Immunohistochemistry with the presence of CD68 and CD163-staining histiocytes within the vessels highlighted by CD31 and ERG.
REACTIVE ANGIOENDOTHELIOMATOSIS WITH INTRAVASCULAR HISTIOCYTOSIS

Discussion

- Reactive angioendotheliomatosis (RAE) is a rare condition, with only 81 cases reported in the literature to date, and only six prior reported cases with intravascular histiocytosis.
- In this case, the patient’s development of livedo reticularis on his thighs several years after first developing RAE on his chest prompted evaluation for a new vasculopathy. RAE may be associated with malignancy, infection, autoimmune disease, and inflammatory conditions, therefore, age-appropriate malignancy screening and screening for infection and co-morbidities is critical. In this case, the additional workup prompted by his development of livedo reticularis was negative, most notably for malignancy and hypercoagulability.
- Histopathology demonstrated a proliferation of small, superficial and focally deep dermal vessels with intravascular proliferation of histiocytes, scattered perivascular T-cells, as well as occasional mast cells.
- Treatment options include topical or oral β-blockers and pentoxifylline. This patient experienced substantial improvement after just 4 months on oral metoprolol. Pulsed dye laser (PDL) may also be considered.

Teaching Points

- While reactive angioendotheliomatosis is rare, it should be considered when evaluating violaceous, vascular-appearing papules on the trunk.
- Diagnosis of RAE is confirmed by histopathology, which can identify both reactive angioendotheliomatosis as well as associated intravascular or intralymphatic histiocytosis.
- The pathogenesis of RAE is unknown; some postulate it may represent a reactive process secondary to vessel occlusion and subsequent tissue hypoxia. β-blockers may treat RAE by inhibition of angiogenesis by downregulation of angiogenic factors such as vascular endothelial growth factor (VEGF) as well as induction of apoptosis of capillary endothelial cells.
- Systemic conditions associated with RAE include underlying malignancy, rheumatologic disease, chronic infection, among other co-morbidities and these should prompt appropriate screening and workup.

References:

CASE 6
A 68-YEAR-OLD WOMAN WITH PHOTOSENSITIVE SKIN RASH

Patient
SM is a 68-year-old woman.

Presenters
Khashayar Afshari, MD, MPH
Maggi Ahmed, MD, PhD
Mehdi Rashighi, MD

History
A 68-year-old female presented with a five-month history of worsening pruritic rash on her face. Over the past two months, she experienced additional extension of the rash to her chest, upper back, elbows, and dorsal hands. In addition, she reported increased sensitivity to sunlight and severe scalp pruritus.

Past Medical History: PVD, lower limb ischemia with left foot amputation, abdominal aortic aneurysm, chronic HCV, IV drug use, hyperlipidemia, hypertension, prediabetes, and cataracts.

Family History: Daughter with autoimmune thyroiditis. Mother with breast and lung cancer.

Allergies: None

Medications: Acetaminophen, aspirin, clopidogrel, pantoprazole, trazodone

Physical Examination
Fair skin with confluent erythematous scaly plaques across the forehead, upper and lower eyelids, and cheeks. Mild edema of the eyelids bilaterally was also noted. Chest and upper back with an erythematous scaly patch in a shawl distribution. Erythematous scaly plaques on the elbows and thighs. Dorsal hand with pink papules overlying the PIP joints. Nail folds with dilated capillary loops and capillary dropout. 5/5 strength in shoulder abduction, elbow flexion and extension, hand grip, and hip flexion. On the dorsum of her right foot, an asymmetric 3x3 mm macule with irregular borders and a blue-grey veil on dermoscopy.

Laboratory Data
- Hb 11.9 g/dL and MCV 77.1 fL
- Fasting blood glucose 122 mg/dL
- Albumin 3.5 g/dL, total bilirubin 0.2 mg/dL, AST 9 U/L and ALT <5 U/L
- Anti-nuclear antibodies, Anti-CADM-140/MDA5 antibodies, and anti-RNP antibodies all positive (Anti-MDA5 antibodies were confirmed by OMRF clinical immunology laboratory)
- Anti-dsDNA antibody indeterminate
- Anti-Smith antibody and anti-chromatin antibody were not detected.
- Malignancy workup: Cancer screening with CEA, CA19-9, and CA-125 were negative. Mammogram and high-resolution chest CT were negative. CT abdomen/pelvis revealed a mass in the right external iliac lymph node that underwent CT-guided biopsy.

Histopathology
- Skin biopsy of the erythematous scaly patch on the thigh showed epidermal atrophy, dyskeratotic keratinocytes, thickening of the basement membrane, and perivascular lymphocytic infiltrate supportive of dermatomyositis.
- The right external iliac lymph node mass pathology revealed metastatic malignant melanoma. Tumor cells were positive for S100, Sox 10, and Melan-A and were negative for BRAF.
- Subsequent right dorsal foot shave biopsy displayed dermal features of regression and focally decreased melanocytes on MART-1 and Sox10 IHC suspicious for regression of a melanocytic lesion.

Treatment
- Hydroxyzine, betamethasone dipropionate 0.05% ointment, pimecrolimus 1% cream
- Methotrexate 25 mg weekly and folic acid daily
- Neoadjuvant pembrolizumab
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**Figure:** Patient had erythematous scaly plaques V-neck sign (a), shawl sign (b), Gottron's sign on elbow (c) and Gottron's papules on dorsal hand overlying the metacarpophalangeal and proximal interphalangeal joints (d), periungual telangiectasias (e), and painful palmar papules (f). Punch biopsy from the right hip (g), asymmetric 3x3 mm macule on right foot (h) with irregular borders and blue-grey veil on dermoscopy (i), and shave biopsy from the right dorsal foot macule (j).
MDA5-POSITIVE DERMATOMYOSITIS ASSOCIATED WITH MALIGNANT MELANOMA

Discussion

- Dermatomyositis (DM) is a rare autoimmune disease that causes significant morbidity through chronic photosensitive rash, intense pruritus, and muscle weakness. Approximately 20% of DM patients lack any clinical or laboratory evidence of muscle involvement (clinically amyopathic DM).
- Patients with adult DM have a significantly higher estimated incidence of cancer, ranging from 5 to 7 times that of the general population.
- Women are affected twice as often as men. Previous studies have indicated that DM disproportionately affects individuals with skin of color and leads to a higher burden of disease.
- Classical findings in cutaneous disease in DM include heliotrope rash, Gottron’s sign and papules, photo-distributed poikiloderma (shawl sign and V-neck sign), cuticular dystrophy, and nail-fold telangiectasias.
- Anti-MDA-5 autoantibody is associated with amyopathic dermatomyositis, and a distinctive cutaneous profile characterized by cutaneous ulceration, palmar papules, oral mucosal pain, and alopecia.
- Although anti-MDA-5 autoantibody presence was confirmed in this patient, it was notable that she lacks the usual vasculopathic changes associated with the MDA-5 skin phenotype.
- Dermatomyositis has been associated with breast, ovarian, and lung cancer. However, its correlation with melanoma is infrequent. Recent research indicates a higher prevalence of paraneoplastic dermatomyositis in advanced stages of melanoma, particularly stage IV, which is indicative of an unfavorable prognosis.

Teaching Points

- The connection between adult dermatomyositis and cancer is firmly established. It is advisable to initiate a cancer workup promptly following a diagnosis of dermatomyositis in adults to screen for any potential associated malignancies.
- Dermatomyositis patients with anti-MDA-5 autoantibody usually present with cutaneous ulceration and are at increased risk for rapidly progressive interstitial lung disease and reduced, yet non-zero, risk of malignancy. Nonetheless, not all patients exhibit the typical MDA-5 phenotypes.
- Although uncommon, dermatomyositis can be associated with malignant melanoma.

References:

CASE 7
A 16-YEAR-OLD GIRL WITH RECURRENT HIGH FEVERS, APHTHOUS ULCERS, AND VARIABLE CUTANEOUS ERUPTIONS

Patient
AR is a 16-year-old girl.

Presenters
Allison Holt, MS IV
Tinian Omere, MS II
Sarah Servattalab, MD
Leah Belazarian, MD

History
A 16-year-old girl with no prior medical history presented to the ED with fever and eroded, crusted papules on the face and trunk. She was diagnosed with probable late-stage VZV. One year later, she presented to the ED and was admitted with fever, abdominal pain, oral and genital ulcers, and tender, crusted plaques on the scalp. Biopsy of an isolated bulla on the right antecubital fossa thought to be due to pathergy from IV insertion revealed sub-epidermal acantholysis with neutrophilic infiltrate. She initially improved with high-dose prednisone but developed a diffuse erythema multiforme (EM)-like eruption and arthralgias when taper was attempted. Biopsy of the eruption revealed subepidermal acantholysis, dyskeratosis, and increased dermal mucin. She was started on a regimen of cyclosporine and hydroxychloroquine, leading to gradual improvement and tapering of prednisone.

Past Medical History: Noncontributory
Family History: Mother passed away in 30s due to heart attack. Parents were consanguineous (1st cousins).

Allergies: None

Medications: Tretinoin 0.025% cream, ketoconazole 2% shampoo, iron 65 mg

Physical Examination
At the time of intial evaluation by dermatology, there was diffuse red erythema and focal crusted plaques of the scalp and conchal bowls with pink erosions of the hard palate and gums. Clear and tense bulla on the right antecubital fossa were noted. After prednisone taper, she developed painful, pink to red erythematous, scaly, eroded papules across the face and neck, chest, abdomen, arms, and legs, which coalesced into plaques on the entire upper back.

Laboratory Data
- CBC notable for hemoglobin 9.6 g/dL (ref range: 11.5-15.3 g/dL)
- CRP 107.9 mg/L (ref: <10 mg/L)
- ESR 64 mm/hr (ref: <20 mm/Hr)
- IL-2 1403.4 pg/mL (ref: 175.3-858.2 pg/mL)
- +SSA >8.0 (ref: <1.0)
- SPEP notable for beta-2 globulin 0.7 g/dL (ref: 0.2-0.5 g/dL), suggestive of acute inflammation
- Negative ANA, dsDNA, anti-Smith, anti-RNP, ANCA, C3-C4, EBV, CMV, HSV1/2, HIV, quantiferon gold, parvovirus PCR. Flow cytometry normal
- HLA-B51 negative
- Dsg1 1.3 u/mL (ref: <18 u/mL), Dsg3 1.4 u/mL (ref: <19 u/mL), envoplakin 0.9 (ref: <1), negative IIF (IgG paraneoplastic pemphigus antibodies) on rat bladder epithelium
- Autoinflammatory disease panel revealed novel heterozygous variant in ANKZF1, which has been associated with early-onset IBD

Imaging and Procedures
- CT chest/abd/pelvis negative
- Full body PET scan negative
- Colonoscopy normal
- Upper endoscopy with scattered duodenal erosions; biopsies positive for H. pylori
- Ophthalmology exam normal

Histopathology
Noted in history above

Treatment
- Dapsone 100 mg daily (Dec 2021 – Mar 2022)
- Cyclosporine 300-400 mg daily (Dec 2021 - Oct 2023)
- Hydroxychloroquine 200-300 mg daily (June 2022 – Oct 2023; Jan 2024 – present)
- Oral prednisone with long taper; course complicated by adrenal suppression
CASE 7
A 16-YEAR-OLD GIRL WITH RECURRENT HIGH FEVERS, APHTHOUS ULCERS, AND VARIABLE CUTANEOUS ERUPTIONS

Figures: (A) A crusted yellow plaque on the conchal bowl with surrounding erythema. (B) Pink to red erythematous, eroded papules with overlying scale coalescing into plaques across the upper back. (C) Shallow pink erosions on the hard palate. (D) Punch biopsy of the right shoulder displayed interface dermatitis, sub-epidermal blister formation, and extensive keratinocyte dyskeratosis. DIF was negative.
AUTOINFLAMMATORY DISORDER OF UNKNOWN ETIOLOGY

Discussion

- No definitive diagnosis to date. Given the constellation of symptoms, concern is high for an autoinflammatory disorder of uncertain etiology. Pyrin-associated autoinflammatory disorder with neutrophilic dermatosis (PAAND) is considered, based on recurrent high fevers, aphthous ulcers, and EM-like eruption.
  - PAAND is a rare monogenic autoinflammatory condition resulting from mutation of the Mediterranean fever (MEFV) gene. This mutation leads to constitutive activation of pyrin, a protein that triggers inflammasome development in response to infection. Upregulation of interleukin-1β results in widespread inflammation, causing episodic fevers, myalgias, arthralgias, and neutrophilic dermatoses (e.g. acne, sterile cutaneous abscesses). GI symptoms including abdominal pain and oral ulcers have also been reported.
  - Prior studies have reported mixed efficacy of anakinra, with one patient noted to have a complete response to therapy and others failing to improve. TNF inhibitors have shown efficacy in some cases.
- The differential includes systemic lupus erythematosus (SLE), Rowell syndrome, Behçet syndrome, and cutaneous manifestations of inflammatory bowel disease. SLE may present with variable skin findings including acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and discoid lupus erythematosus (DLE). The majority of patients with ACLE and SCLE will have a positive ANA, while those with DLE may not. Rowell syndrome is a rare presentation of lupus with continued debate surrounding its classification and diagnosis. It is characterized by erythema multiforme-like lesions and marked by several immunologic factors including "speckled type" ANA, anti-Ro/SSA, anti-LA/SSB, and positive RF.
  - In favor of SLE, our patient has oral ulcers, anemia, +SSA, and EM-like lesions with increased dermal mucin on biopsy, though ANA was negative. Rheumatology favored ANA-negative lupus, but noted that worsening rash despite the initiation of high-dose prednisone was unexpected. She ultimately improved on hydroxychloroquine, lending further support to a diagnosis of lupus.
  - Rowell syndrome, specifically, should be considered, given the EM-like pattern of skin involvement and supporting biopsy findings of a vacuolar interface dermatitis with combined features of erythema multiforme and lupus erythematosus.
  - In addition to Middle Eastern ethnicity, the features of Behçet syndrome that our patient exhibits include recurrent oral and genital ulcers and EM-like findings. Though she meets the International Criteria for Behçet Disease (ICBD), HLA-B51 testing was negative; however, this is not necessary for diagnosis.

Teaching Points

- Autoinflammatory diseases are a diverse group of disorders typically caused by a single gene mutation and characterized by widespread inflammation; these should be considered in patients with recurrent inflammatory episodes in the absence of an underlying cause.
- Lupus, including cutaneous variants of SLE, typically responds well to hydroxychloroquine and should be considered in the differential diagnosis of autoinflammatory disease.
- Rowell syndrome is a controversial diagnosis with persistent debate surrounding diagnostic criteria; it may be considered in patients presenting with EM-like lesions in the setting of an underlying lupus erythematosus.

References:
CASE 8
A 65-YEAR-OLD WOMAN WITH RECURRENT SEBACEOUS MALIGNANCIES

Patient
DC is a 65-year-old female.

Presenters
Emily Meara, MSIII
Shauna Rice, MD
Fnu Nutan, MD

History
A 65-year-old woman presented to clinic after diagnosis of Muir-Torre syndrome in association with hereditary nonpolyposis colorectal cancer and biopsy-proven sebaceous adenoma of the left eyelid. She was referred to dermatology for identification of additional lesions suspicious for malignancy. The biopsy of a lesion on the upper back revealed sebaceous adenoma. In the following years (2012-present), she was diagnosed with several more sebaceous adenomas as well as numerous sebaceous carcinomas of the face. At a recent visit (2023), she presents for evaluation of multiple new bleeding lesions on the face.

Past Medical History: HIV on triple therapy, hepatitis C, squamous cell carcinoma of the larynx, Muir-Torre/Lynch syndrome, invasive mucinous adenocarcinoma of the colon (8/2010), tubular adenoma of rectum with high grade dysplasia (7/2010), coronary artery disease, hypothyroidism, COPD, hyperlipidemia, hypertension

Family History: Mother with colon cancer died at age 52, two brothers with Hodgkin lymphoma, CAD in paternal side of family, three male children with unknown genetic status.

Allergies: Ibuprofen, ribavirin, interferon alfa-2a, acetaminophen-codeine

Medications: Atorvastatin, buspirone, clonazepam, gabapentin, levothyroxine, lisinopril, olanzapine, omeprazole, buprenorphine/naloxone, budesonide/formoterol, abacavir/dolutegravir/lamivudine, umeclidinium, albuterol HFA

Physical Examination
General: Well-appearing woman with nasal cannula in place
Skin: On the left nasal ala, left chin, and right cheek there are three reddish-brown exophytic pedunculated nodules with overlying hemorrhagic crust. On the rest of the face there are scattered pink to yellow papules.

Laboratory Data
- Absolute CD4 count 304, HIV-1 RNA Quant PCR <20
- Genetics workup: positive high-level microsatellite instability, positive loss of expression of MSH2 and MSH6 proteins

Histopathology
2012: Biopsy of left upper back revealed a tumor composed of mature sebaceous glands with minor basaloid cells. No significant cytologic atypia observed. Immunohistochemistry studies show that the tumor has loss of MLH2 and normal expression of MLH1, consistent with the history Muir-Torre syndrome.
2023: Shave biopsies from the nose, chin, and right cheek displayed mitotically active, infiltrative lobules of basaloid and sebaceous cells with central comedonecrosis

Treatment
- Excision or Mohs micrographic surgery of all sebaceous carcinomas
- Frequent skin checks every 6 months
- Regular follow up with ophthalmology given lesion on left conjunctiva, oncology, gastroenterology, and infectious disease
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A 65-YEAR-OLD WOMAN WITH RECURRENT SEBACEOUS MALIGNANCIES

Figure: (A) and (B): Left nasal ala, left chin, and right cheek with reddish-brown exophytic and pedunculated nodules with overlying hemorrhagic crust; (C) and (D): Shave biopsies of nodules on nose, cheek and right chin.
**MUIR-TORRE SYNDROME**

**Discussion**

- Sebaceous adenomas are benign tumors, while sebaceous carcinomas are rare and aggressive malignancies derived from sebaceous glands. Clinically, sebaceous adenomas appear as yellowish, painless, round papules often on the eyelid or nose, whereas sebaceous carcinomas are reddish-brown tumors that may be ulcerated.
- Histologically, sebaceous adenomas are defined by mature, well-circumscribed sebaceous lobules with peripheral basaloid cells surrounded by a fibrous pseudo-capsule. Sebaceous carcinomas demonstrate similar proliferation of sebaceous cells and basaloid cells with features concerning for malignancy such as pleomorphism, mitotic figures, hyperchromatism, and necrosis.
- Both sebaceous adenomas and sebaceous carcinomas are highly associated with Muir-Torre syndrome (MTS).
- Muir-Torre syndrome is autosomal dominantly inherited deficiency in genetic repair mechanisms, including the mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2), which lead to microsatellite instability. MTS is a phenotypic variant of hereditary nonpolyposis colorectal cancer syndrome (HNPCC; Lynch syndrome) making up about 9% of those with Lynch syndrome (LS).
- Clinical diagnostic criteria of MTS include one or more of the following: first sebaceous neoplasm at age less than 60, presence of one or more sebaceous neoplasms, personal or family history of Lynch-related malignancy.
- Keratoacanthomas are also commonly seen in patients with MTS.
- The most common internal malignancy in Muir-Torre is colon cancer. Other associated malignancies include cervical, endometrial, brain, pancreatic, and lung cancer.
- Incorporation of tumor immunohistochemistry MMR screening into the management of sebaceous carcinomas may increase the opportunity for MTS diagnoses for patients who may benefit from cancer surveillance and immunotherapy treatment targeted to MTS/LS cancers.

**Teaching Points**

- Sebaceous adenomas and carcinomas are considered markers of Muir-Torre syndrome and should raise suspicion for a possible hereditary cancer syndrome. Sebaceous adenomas are benign and may be managed conservatively. Those found to have a sebaceous carcinoma should undergo wide local excision or Mohs micrographic surgery with potential lymph node biopsy depending on the size and location of the lesion. Immunohistochemistry should also be performed on all sebaceous carcinomas to evaluate for microsatellite instability.
- Biopsy proven sebaceous malignancy should prompt referral to oncology for further malignancy workup and possible genetic testing.
- In patients with HIV and MTS, diligent treatment with antiretroviral therapy is crucial as some evidence suggests that states of immunodeficiency can exacerbate the number and severity of cutaneous malignancies in MTS.
- Children born to a parent with MTS have a 50% chance of inheriting the mutation. Family members of those diagnosed with MTS/LS should be offered genetic testing by the age of 20-25 to guide management.
- Management of Muir-Torre syndrome demonstrates the importance of interprofessional team collaboration for comprehensive patient care.

**References:**

CASE 9
A 77-YEAR-OLD MAN WITH WELL-DEFINED, ASYMPTOMATIC NODULES ON BILATERAL FEET

Patient
RN is a 77-year-old man.

Presenters
Nicole Loranger, MSIV
Carolyn Foley, MSII
Holly Neale, MD
Ryan M. Svoboda, MD, MS

History
A 77-year-old man with ankylosing spondylitis presented with multiple asymptomatic pink well-demarcated nodules on his bilateral feet and ankles. The nodules developed three years prior to presentation and were stable without pain, bleeding, or new lesions. The knees and elbows were unaffected. He had no systemic symptoms. Outside shave biopsy showed a mixed inflammatory process, granulation tissue, and fibrosis. After an incisional biopsy of the left lateral ankle, many left-sided nodules became purpuric and tender. Once the inflammation improved, his left foot nodules were treated with intralesional triamcinolone. This initially provided relief, but purpura and pain recurred post-procedurally to the treated sites. This resolved over a two-month treatment holiday. The right foot nodules remained asymptomatic.

Past Medical History: Ankylosing spondylitis, osteoarthritis, hypertension, hyperlipidemia, type II diabetes, benign prostatic hyperplasia, coronary artery disease, thoracic aortic aneurysm, gastro-esophageal reflux disease, paroxysmal tachycardia, intertrigo.

Family History: Noncontributory

Allergies: None

Medications: Adalimumab, ammonium lactate cream, aspirin, atorvastatin, carvedilol, cyclobenzaprine, empagliflozin, ketoconazole shampoo, metformin, nitroglycerin, omeprazole, simvastatin, tramadol, trazodone, and triamcinolone 0.025% ointment.

Physical Examination
Multiple non-tender nodules over the bilateral feet, including plantar surface and ankles. One nodule overlying the left calcaneus with slight surface erosion. On the right foot are several slightly pink nodules without purpura or tenderness.

Laboratory Data
- CBC with differential: unremarkable
- CMP: unremarkable
- ANA/ANCA screen: negative
- Protein electrophoresis (serum): B2 globulin 0.8 g/dL (H)
- Serum immunofixation: negative for monoclonal proteins
- Protein electrophoresis (urine): unremarkable
- HIV1/2 Ag/Ab: non-reactive
- Hepatitis B: surface Ag/core Ab non-reactive
- Hepatitis C: non-reactive
- Urinalysis: 3+ glucose, no protein

Histopathology
- Left lateral ankle punch biopsy (March 2023) showed benign hyperkeratotic epidermis with cicatricial dermal fibrosis and lympho-histiocytic infiltrate.
- Left lateral ankle incisional biopsy (April 2023) displayed dense dermal fibrosis in a multinodular to storiform pattern. Abundant neutrophils, histiocytes, and eosinophils were present. Infectious stains were negative for microorganisms.

Treatment
- Doxycycline monohydrate 100 mg BID
- Minimize trauma with well-fitting footwear
- Triamcinolone intralesional injection (initial: 20 mg/mL, increased to 40 mg/mL at second and third injection) to five left foot fibrotic nodules
- Clobetasol 0.05% ointment BID
- Wound care including DuoDERM dressing, Mepilex dressing, and mupirocin ointment to open wound areas
CASE 9
A 77-YEAR-OLD MAN WITH WELL-DEFINED, ASYMPTOMATIC NODULES ON BILATERAL FEET

Figure: (A) Discrete asymptomatic pink nodules on the left lateral foot; nodule over left lateral malleolus was incisional biopsy site. (B) Purpuric discrete nodule on the medial left foot (following incisional biopsy to ipsilateral but distinct lesion overlying left lateral malleolus). (C) Pink and skin colored nodules on the plantar surface of bilateral feet. (D) H&E (left ankle incisional biopsy): dense dermal storiform fibrosis with abundant neutrophils, histiocytes, and eosinophils.
FIBROTIC ERYTHEMA ELEVATUM DIUTINUM

Discussion

- Erythema elevatum diutinum (EED) is a rare form of leukocytoclastic vasculitis that can present in adults of any sex, race, or ethnicity. It is most often reported in the fourth through sixth decades of life, though patients with HIV may present earlier. Fewer than 1000 cases have been reported.
- EED is characterized by red to violaceous papules, plaques, and nodules distributed symmetrically across extensor surfaces and acral sites. Though often asymptomatic, these lesions may be accompanied by pain or burning sensations; arthralgias, fever, and ocular symptoms may also be present.
- While EED has no clear etiology, it is frequently reported in the setting of preexisting systemic disease, particularly HIV, MGUS/myeloma, irritable bowel disease, celiac disease, and various autoimmune conditions. While our patient does not have one of these associated conditions, he does have a history of ankylosing spondylitis which could have been the trigger of his skin disease. To our knowledge, there is one other report of EED in the setting of ankylosing spondylitis.
- The histopathology of early stage EED reveals leukocytoclastic vasculitis with polymorphonuclear infiltrate. In contrast, mature lesions, as in this case, are less common and may exhibit more fibrosis, granulation tissue, and small vessel proliferation. Direct immunofluorescence may help with identification of vasculitis.
- The differential diagnosis may include Sweet syndrome, atypical infection, soft tissue tumors, erythema multiforme, granuloma annulare, sarcoidosis, rheumatoid nodules, and xanthomas.
- Spontaneous resolution is often seen after 5-10 years, though patients may opt for local or systemic treatment.
- Dapsone is considered a first-line systemic treatment option. Given the lack of active vasculitis, dapsone was initially deferred in this case. Interestingly, after the patient developed pain and purpura in multiple ipsilateral previously asymptomatic lesions following incisional biopsy, dapsone was re-considered given concern for reactivation of vasculitis. Dapsone was ultimately deferred when this phenomenon resolved (after a course of doxycycline for post-biopsy inflammation). Local therapy with intralesional and topical steroids was selected for chronic fibrotic/nodular disease. Interestingly, intralesional therapy again led to development of pain and apparent purpura, which also resolved after cessation of treatment.
- To our knowledge, there are no reports of EED flaring after procedural intervention (i.e., biopsy or intralesional triamcinolone), as in this case, which we postulate as a possible underlying trigger for the pain and purpura of previously asymptomatic lesions this patient developed.

Teaching Points

- EED is a rare vasculitis that presents as red, brown, or violaceous papules or nodules, usually located near joints. Careful clinicopathological correlation is advised given potential clinical and histologic mimickers.
- Patients with EED often have pre-existing infectious, inflammatory, or hematologic conditions, warranting appropriate review of systems and labs.
- Dapsone is the most commonly used treatment for EED, though it may be less effective in nodular disease and discontinuation may result in lesion recurrence. Tetracyclines, colchicine, NSAIDs, and chloroquine may also be used. Topical and intralesional steroids can be considered in skin-limited cases.
- Treatment of potential triggers, including antiretrovirals for HIV and plasmapheresis for IgA paraproteinemia, may also aid in the resolution of EED. Given time, EED may resolve without treatment.

References:
CASE 10
A 38-YEAR-OLD WOMAN WITH CHRONIC PROGRESSIVE SKIN TIGHTENING, WEAKNESS AND ATROPHY OF HER BILATERAL UPPER AND LOWER EXTREMITIES

Patient
MT is a 38-year-old female.

Presenters
Jane Chuprin, MSIII/PhD candidate
Sina Foroutanjazi, MD
Mehdi Rashighi, MD

History
A 38-year-old woman presented to our clinic with worsening skin tightening, atrophy, and weakness of her arms and legs. Her skin tightening started in childhood. At age 12, she had an episode of fever, lethargy, weight loss, joint pain, and muscle weakness, at which time an elevated absolute eosinophil count of 7500 (34%) was noted. The diagnosis was made via a skin and fascia biopsy. For several years afterward, she was treated with pulsed IV methylprednisolone, oral prednisone, oral or subcutaneous methotrexate, and physical therapy. She was intermittently lost to follow-up for several years and received no treatment. She represented again at aged 17 with new pink firm plaques on her face and body. After a repeat punch biopsy, she was restarted on prednisone and methotrexate. Several years later, she was evaluated in rheumatology for her joint pain and weakness, but given her original diagnosis she was referred back to dermatology and was eventually seen in the Connective Tissue Clinic.

Past Medical History: Asthma, Type 2 diabetes, hyperlipidemia, strabismus, bipolar disorder, anxiety, post-traumatic stress disorder

Family History: Noncontributory

Allergies & Drug Reactions: Methotrexate (elevated LFTs), Imatinib (nausea), Penicillin V (anaphylaxis), Codeine (swelling), Carrot (dyspnea), Shellfish

Medications: Metformin, glipizide

Physical Examination
Skin: Generalized tightening of the skin with reduced skin tenting on the neck, arms, and legs, with positive groove sign. Multiple hard subcutaneous nodules on the bilateral forearms and shins. Nailfold capillaroscopy unremarkable.

MSK: Reduced range of motion of bilateral ankles with subjective tenderness. Muscle atrophy of the upper and lower extremities.

Laboratory Data
- Negative SSA/SSB, Anti-Smith Ab, ds-DNA Ab, Anti-centromere Ab (2017)
- Negative ANA (2022)
- Negative Anti-Scl-20 (2022)
- ESR 33 (2023)
- Eosinophil count 2.2% (2024)

Histopathology
- Skin and fascia punch biopsy of right lateral distal leg in 1998: mononuclear cell infiltrate with many eosinophils and focal fibrosis of the fascia and striated muscle. No evidence of vasculitis, epithelioid granuloma, parasites, or muscle degeneration
- Skin biopsy of left hip in 2003: pansclerotic morphea

Treatment
- Mycophenolate mofetil 1000 mg twice daily, with plan to increase to 1500 mg twice daily if tolerated
- Start physical therapy
CASE 10
A 38-YEAR-OLD WOMAN WITH CHRONIC PROGRESSIVE SKIN TIGHTENING, WEAKNESS AND ATROPHY OF HER BILATERAL UPPER AND LOWER EXTREMITIES

Figure: (A) and (B) Right and left arms demonstrating skin tightening. Note the skin tenting (dimpling) around the right humerus (A).
(C) Bilateral legs exhibiting skin tightening and groove sign (skin depression along superficial veins).
(D) Closeup of right lateral thigh exhibiting groove sign.
(E) Bilateral arms showing groove sign (best visualized with limbs are raised).
(F) Closeup of left arm exhibiting skin tightening.
(G) Skin tenting around the right nuchal region.
 EOSINOPHILIC FASCIITIS

Discussion

- Eosinophilic fasciitis (EF), also known as Shulman Syndrome, is regarded as a more severe condition on the morphea spectrum. However, EF should not be considered to be synonomous with morphea, as EF includes inflammation of the fascia and potential for peripheral eosinophilia.
- The etiology of EF is unclear, but it is considered to be due to an auto-inflammatory process leading to extensive extracellular matrix deposition.
- The incidence and prevalence of EF is unknown.
- EF can have a similar presentation to systemic sclerosis; however, EF differs from systemic scleroderma by the absence of sclerodactyly, Raynaud’s phenomenon, nail fold capillary changes, and negative anticientromere antibodies.
- The upper and lower extremities are typically affected in EF. The neck and trunk may also be involved in more extensive cases.
- Systemic signs and symptoms such as weight loss, asthenia, and adjacent myositis may also occur in EF.

Teaching Points

- EF may often be diagnosed clinically. However, the gold-standard diagnostic method for EF is a full-thickness skin biopsy involving the fascia and muscle tissue. MRI is a non-invasive alternative diagnostic option.
- Early EF may present with pitting edema, elevated inflammatory markers, and peripheral eosinophilia, but these findings might be transient and not always present.
- In EF, histology should demonstrate fasciitis, meaning immune cells (lymphocytes with eosinophils, plasma cells and macrophages) infiltrating thickened fascial tissue. Eosinophils may only be present transiently, especially if the patient is given systemic steroids or immunosuppressive drugs.
- The combination of systemic corticosteroids and methotrexate are first-line therapies for EF, including juvenile EF. However, other treatment options, including mycophenolate mofetil, have been used for refractory and relapsing disease.

References:

CASE 11
AN 82-YEAR-OLD MAN WITH SCALY PINK PLAQUES ON ABDOMEN AND LOWER EXTREMITIES

Patient
BR is an 82-year-old man.

Presenters
Ryan Chen, MSIII
Sina Foroutanjazi, MD
Ryan Svoboda, MD, MS

History
An 82-year-old man initially presented in 2019 with erythematous scaly, pruritic plaques involving the trunk and extremities. Biopsy revealed an epidermotropic atypical lymphocytic infiltrate and many large cells with significant CD30 positivity. Interestingly, the infiltrate was partially CD4+, but CD4 staining was not extensive. He was initially diagnosed with mycosis fungoides with partial CD4+ expression and CD30+ large cell transformation. He was treated with brentuximab vedotin for a total of 7 cycles concurrently with nbUVB phototherapy from January to June 2020. He achieved complete remission.

In October 2021, he experienced a relapse of his skin lesions, which presented as large annular plaques on his extremities. Repeat biopsy demonstrated T-cell infiltrate with significant epidermotropism and a similar immunohistochemical staining pattern again felt to be consistent with mycosis fungoides. He was treated with 6 cycles of mogamulizumab from November 2021 to April 2022 and had an excellent response.

In December 2022, the patient developed another apparent clinical recurrence on the abdomen and left lower extremity. A shave biopsy was performed.

Past Medical History: Warthin tumor of parotid gland, COPD, pre-diabetes, CKD, HTN, HLD

Family History: Noncontributory

Allergies: Iodinated contrast media (urticaria)

Medications: Allopurinol, chlorthalidone, gabapentin, ketoconazole 2% cream, simvastatin, triamcinolone acetonide 0.1% cream

Physical Examination
General: Well appearing, slightly fatigued, but in no acute distress
Skin: Three pink, finely scaling patches with cigarette paper atrophy on the left lower quadrant of the abdomen were noted. There was a large, deep, pink, scaly thin plaque on the left lateral calf. There was a circular pink plaque with fine scale on the left medial calf. Approximately 2% BSA was affected with a similar morphology.

Laboratory Data
- Normal WBC, no eosinophilia
- BUN 37 (elevated), creatinine 1.51 (elevated)
- LDH 160 (normal)

Histopathology
Shave biopsies from the left lower extremity revealed an epidermotropic infiltrate of small to medium sized atypical CD30+ T-cells which were both CD4/CD8 negative. Shave biopsy from abdomen revealed similar population of null (CD4/CD8 double negative) lymphocytes. Due to the unusual null staining pattern, further IHC workup was requested by the clinician which revealed positive TCRγδ and negative TCR-βF1 expression.

Treatment
- Started on oral bexarotene 225 mg daily, increased to 300 mg daily, subsequently discontinued due to significant disease progression with >30% BSA involvement of thick plaques. Patient was transitioned to IV romidepsin with good response.
CASE 11
AN 82-YEAR-OLD MAN WITH SCALY PINK PLAQUES ON ABDOMEN AND LOWER EXTREMITIES

Figure: (A) Dark pink patches and plaques with fine scale on abdomen and chest. (B) Dark pink patches and plaques with thin scale on bilateral feet, ankles, and anterior shins. (C) Punch biopsy from the left shin displayed marked spongiosis with a dense, atypical, epidermotropic, small to medium-sized lymphocytic infiltrate. Lymphocytes were further characterized as CD3 and CD30 positive, and CD4, CD8, CD7, perforin, TIA-1, and CD56 negative. Notably, lymphocytes are positive for TCR delta, and negative for TCR BF1.
MYCOSIS FUNGOIDES WITH GAMMA DELTA PHENOTYPE

Discussion

- Mycosis fungoides (MF) is the most common primary cutaneous T-cell lymphoma (CTCL) and presents in older adults with a 2:1 predilection for males and a median incidence between 55 and 60 years of age. Clinical features include an indolent eruption of erythematous, scaly, plaques and patches, which often resemble common skin disorders such as atopic dermatitis and psoriasis. Histology is characterized by epidermotropic infiltrates of atypical lymphocytes with irregular cerebriform nuclei. Tumor cells in MF commonly express T-helper memory cell phenotype (CD4+, CD8–) with monoclonal T-cell receptor gene rearrangements.

- Primary cutaneous γδ T-cell lymphoma (PCGDTL) is a rare, aggressive subtype of CTCL that is typically CD4 and CD8 negative and expresses a cell surface γδ T-cell receptor heterodimer. Clinical features can include subcutaneous nodules resembling panniculitis (panniculitic variant arising from Vdelta-2 cells) or extensive and often ulcerated plaques (dermal variant arising from Vdelta-1 cells); patients may occasionally experience B symptoms. PCGDTL has a poor prognosis and an estimated 5-year survival rate of 19.9%.

- Currently, the World Health Organization/European Organization for the Research and Treatment of Cancer recommend that patients such as ours who present with a dermatosis clinically representing classic mycosis fungoides but with immunohistochemical evidence of a γδ phenotype be classified as MF rather than PCGDTL. However, there have been reports of patients with MF with a γδ phenotype subsequently progressing to a more aggressive clinical picture resembling PCGDTL, so the true significance of a γδ phenotype in otherwise classic MF remains unclear.

- There is no clear evidence whether routine testing for γδ TCR has a clinical benefit in patients with otherwise classic MF, but it should be considered in patients with unusual immunophenotypes (e.g., CD4/CD8 null).

- Management is based on individual disease characteristics and response to therapy. Treatment includes a combination of skin-directed and systemic approaches. Skin-directed treatment may include corticosteroids, chemotherapy, phototherapy, and localized radiation. Systemic approaches may include retinoids, chemotherapy, and novel targeted therapies. While treatment is generally identical to that of classic MF, close observation is likely warranted.

Teaching Points

- MF classically has a CD4+/CD8- phenotype. CD4/CD8 null phenotype may be present in MF subvariants or PCGDTL. It is important to clinically differentiate between MF and PCGDTL based upon lesion morphology and tempo of disease, given that the latter is known to have an aggressive course. Currently, MF with γδ phenotype is considered a form of classic MF rather than a variant of PCGDTL, but a better understanding of the pathogenesis and clinical course of this relatively recently recognized entity is needed.

- Recognition of rare clinical and pathologic variants of MF is important as they are often initially misdiagnosed. Immunophenotypic characterization of CTCL is crucial to prevent misdiagnosis, to allow for more optimal outcomes research and a better understanding of prognosis, and to ensure patients receive appropriate care.

- The association of γδ phenotype and prognosis is relatively unclear. While patients appear to have an indolent course akin to classic MF, there have been reports of patients progressing to a more fulminant presentation. Patients may require close surveillance or repeat biopsies of suspicious lesions to monitor for potential progression to more aggressive disease.

References:

CASE 12
A 60-YEAR-OLD WOMAN WITH PAINFUL INDURATED PLAQUES ON BILATERAL THIGHS AND LEGS

Patient
SE is a 60-year-old female.

Presenters
Stephanie Choi, MSIII
Jessica Orofino, MSII
Mary Awad, MD
Ryan Svoboda, MD, MS

History
A 60-year-old female presented to the clinic with a two-week history of painful indurated pink plaques on bilateral thighs and legs. The eruption initially appeared as four mildly tender plaques on her bilateral medial thighs and progressed to her bilateral lateral thighs and proximal calves. The patient initially denied systemic symptoms, although later developed new right-sided tremor and fatigue. An outside dermatology clinic performed a punch biopsy with inconclusive results and diagnosed her clinically with panniculitis, for which she was prescribed a course of prednisone that was completed two days prior to presentation. A repeat punch biopsy revealed increased dermal and subcutaneous mucin and lipomembranous change, but with focal areas of CD8+ lymphocytes rimming adipocytes. An incisional biopsy was performed for a more definitive diagnosis.

Past Medical History: Autism spectrum disorder, abnormal uterine bleeding s/p hysterectomy, depression with anxiety, hyperlipidemia, hyperparathyroidism, medullary sponge kidney disease, nephrolithiasis

Family History: Father with coronary artery disease, paternal grandfather with seizure disorder

Medications: Benzonatate, cholecalciferol, escitalopram, ferrous sulfate, hydrochlorothiazide, loratadine, multivitamin with minerals, pravastatin, potassium citrate, sulfamethoxazole/trimethoprim; prednisone completed two days prior to presentation (40 mg PO once daily for 5 days, followed by 10 mg taper every 5 days).

Allergies: None

Physical Examination
Pink indurated erythematous plaques on medial and lateral thighs, bilaterally. Indurated pink plaques on bilateral posterior legs, more prominent on right leg. Two erosions on inner thighs, consistent with prior biopsy sites.

Laboratory Data/Imaging
- ANA positive (abnormal; 1:640, 1:320)
- WBC 3400/µL (low), Hgb 9.3 g/dL (low), Hct 21.1% (low)
- AST 46 U/L (high), ALT 54 U/L (normal)
- Triglycerides 115 mg/dL (normal)
- Ferritin 1518 ng/mL (high), Fibrinogen 531 mg/dL (high), LDH 392 U/L (high)
- CRP 4.2 mg/L (high), ESR 35 mm/hr (high)
- Soluble CD25 2065.3 pg/mL (high)
- SSA, SSB, RNP, anti-DSDNA antibodies negative (normal)
- PET/CT: Unremarkable. No nodal or visceral involvement.

Histopathology
Incisional biopsy for H&E from left thigh demonstrates atypical subcutaneous lymphoid infiltrate with extensive necrosis, prominent rimming of adipocytes by CD8 positive atypical cells with elevated Ki-67, and notable mucin. TCR immunohistochemistry revealed positive beta-F1 staining and negative delta staining. T-cell clonality assay was positive for TCR gamma chain rearrangement. Overall, this supports the diagnosis of subcutaneous panniculitis-like T-cell lymphoma.

Treatment
- Methotrexate 15 mg PO once weekly for one week, increased to 25 mg after
- Folic acid 1 mg PO once daily
- Mupirocin 2% ointment daily with dressing changes on thigh
CASE 12
A 60-YEAR-OLD WOMAN WITH PAINFUL INDURATED PLAQUES ON BILATERAL THIGHS AND LEGS

Figure: (A) Pink, indurated, erythematous plaques on right lateral thigh and (B) bilateral medial thighs. (C) Biopsy demonstrating atypical subcutaneous lymphoid infiltrate with a prominent rim of adipocytes by CD8+, TCR βF1+ atypical T-cells and focal fat necrosis.
**SUBCUTANEOUS PANNICULITIS-LIKE T-CELL LYMPHOMA**

**Discussion**
- Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare form of non-Hodgkin lymphoma characterized by the neoplastic invasion of CD8+ TCRα/β T-cells into subcutaneous tissue.
- SPTCL presents as painless subcutaneous plaques and nodules with overlying erythema, commonly on the lower extremities, upper extremities, or trunk. About 50% of patients have systemic symptoms.
- While SPTCL overall has a favorable prognosis, about 24% of cases are complicated by hemophagocytic syndrome (HPS), which is a life-threatening systemic disease characterized by prolonged fever, cytopenia, transaminitis and hepatosplenomegaly. Lab findings include elevated triglycerides, ferritin, transaminases, bilirubin, and lactate dehydrogenase and decreased fibrinogen. Hemophagocytic lymphohistiocytosis (HLH) is a subset of HPS that can cause elevated serum soluble CD25 levels at a median of 10,000 U/mL.
- Differential diagnosis includes erythema nodosum, infectious panniculitis, lupus erythematosus panniculitis (LEP), primary cutaneous γ/δ T-cell lymphoma, and natural killer T-cell lymphoma.
- In our case, it was particularly challenging to differentiate between SPTCL and LEP due to overlapping features of SPTCL (atypical CD8 T-cells) and LEP (dermal mucin deposition and plasma cells) in the pathology reports and the patient’s ANA positivity. However, given the degree of atypical lymphocytes noted in repeat tissue biopsy and the overall clinical picture (lesion distribution and age), the patient’s findings were most consistent with SPTCL. Laboratory findings and neurologic findings were concerning for possible evolving HLH, but given normalization of abnormal lab values after initiation of treatment, decision was made in conjunction with oncology to defer bone marrow biopsy.

**Teaching Points**
- SPTCL is difficult to differentiate from LEP. Clinically, LEP presents more commonly on the face and proximal extremities, whereas SPTCL is more frequently distributed on the lower extremities, upper extremities, or trunk. Systemic findings such as hepatosplenomegaly may favor SPTCL.
- Pathology can help differentiate between SPTCL and LEP. Histologically, SPTCL is characterized by a dense infiltrate of neoplastic, monoclonal, CD8 β F1 T-cells that surround adipocytes, with a high Ki-67 proliferation index. In contrast, LEP generally presents with epidermal and dermal changes, intradermal mucin, and a mixture of inflammatory cells including CD4/CD8 T-cells, lymphoid follicles, plasma cells, and aggregates of plasmacytoid dendritic cells. Two reliable histopathological features of LEP that distinguish it from SPTCL include the absence of atypical T-cells and a low Ki-67 proliferation index.
- SPTCL alone has an excellent prognosis with an 82% 5-year disease-specific survival rate. The concurrence of HLH worsens the prognosis significantly with a 46% 5-year overall survival rate.
- There is no standardized treatment for SPTCL. Immunosuppressive therapy, such as methotrexate and systemic corticosteroids are often used as first-line treatments. In cases of refractory or relapsed SPTCL, cyclosporine A, pralatrexate, and histone deacetylase inhibitors can be considered. In severe cases of SPTCL, or those associated with HLH, anthracycline-based chemotherapy regimens, high dose corticosteroids with cyclosporine A, and ruxolitinib can also be considered.

**References:**
CASE 13
AN 85-YEAR-OLD WOMAN WITH A PRURITIC, BLEEDING PLAQUE ON THE LEFT LABIA MAJORA

Patient
AL is an 85-year-old woman.

Presenters
Jenny Chung, MSI
Alice Tan, MSIV
Shauna Rice, MD
Ryan Svoboda, MD, MS

History
An 85-year-old woman presented in March 2023 with a 3-month history of a pruritic, bleeding, raised plaque of the left labia majora, with extension to the labia minora. She had not treated this area with any therapies. The patient’s history was pertinent for Stage IB mycosis fungoides (MF), diagnosed in 2012 and previously treated with nbUVB phototherapy. She is currently treating with oral bexarotene and topical steroids, with stable disease since 2017.

Past Medical History: Mycosis fungoides (stage IB at diagnosis, current TNMB classification T1aN0M0B1b, total BSA 2%), multiple non-melanoma skin cancers (>10) and dysplastic nevi, papillary thyroid cancer s/p total thyroidectomy in 2016, hypertension, hypercholesterolemia, left carotid stenosis

Family History: Noncontributory

Allergies: Methylparaben sodium, betamethasone dipropionate

Medications: Amlodipine, atorvastatin, bexarotene 150 mg daily, hydrochlorothiazide, levothyroxine, triamcinolone 0.1% cream

Physical Examination
Skin: On the left labia majora, there is a crusted pink plaque with overlying macerated white papules.

Lower back and right abdomen show faint pink patches, ~5% BSA.

Lymph nodes: There is no clinically palpable cervical, axillary, inguinal, or epitrochlear lymphadenopathy.

Laboratory Data
- Normal CBC
- Increased LDL cholesterol and triglycerides (stable)
- Low TSH (expected in setting of bexarotene), normal T4

Histopathology
Shave biopsy from the left labia majora displayed large, pale intraepidermal cells with glandular differentiation and prominent pagetoid spread, staining positive for CK7 (shown) and CAM5.2, consistent with Extramammary Paget disease. Left vulvectomy revealed numerous small foci of superficial invasion (<0.1cm depth) in background of extensive Paget disease with adnexal involvement and marked chronic inflammation. Paget disease (in situ) spans 5 cm in greatest dimension.

Treatment
- Urgent referral to gynecologic oncology for surgical management
- Referral for colonoscopy, mammography, and Pap smear to assess for synchronous internal malignancies
- Continue bexarotene 75 mg twice daily
- Continue triamcinolone 0.1% cream twice daily to active areas of involvement
CASE 13
AN 85-YEAR-OLD WOMAN WITH A PRURITIC, BLEEDING PLAQUE ON THE LEFT LABIA MAJORA

Figure: (A) Left labia majora with pink crusted plaque and overlying white macerated papules. (B) Abdomen with faint pink patches. (C) and (D) Shave biopsy from left labia majora. (E) CK7 positive staining.
Discussion

- Mycosis fungoides (MF) is the most common form of cutaneous T-cell lymphoma, accounting for nearly 50% of all primary cutaneous lymphomas.
  - Early-stage MF typically presents in sun-protected areas. Lesions are typically polymorphic and can present as patches, plaques, tumors, or less commonly, erythroderma.
  - Histopathology typically reveals an epidermotropic infiltrate of cerebriform CD4+ lymphocytes with a reactive band of CD8+ lymphocytes in the superficial dermis. Thicker plaque and tumor-stage lesions feature prominent dermal involvement.
  - Early-stage MF often mimics benign inflammatory dermatoses, with the differential diagnosis including atopic dermatitis, allergic contact dermatitis, psoriasis, actinic reticuloid, and drug eruption. Other primary cutaneous lymphomas such as primary cutaneous anaplastic large cell lymphoma, dermal primary cutaneous gamma-delta T-cell lymphoma, and aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma can be mistaken for MF. Sezary syndrome can clinically look identical to erythrodermic MF.
  - Patients with MF have an increased risk of secondary primary malignancies (particularly hematologic) and should be evaluated based on signs and symptoms in addition to age-appropriate malignancy screenings.

- Extramammary Paget disease (EMPD) is a rare intraepithelial adenocarcinoma affecting areas of abundant apocrine glands including the vulvar, perineal, scrotal, and penile skin, and can be primary or secondary in etiology.
  - Patients may present with erythematous, well-demarcated, scaly, and/or ulcerated plaques. Lesions are classically pruritic, but burning, pain, and edema can also occur.
  - Histopathology demonstrates the presence of Paget cells (atypical large cells with abundant clear cytoplasm and large pleomorphic nuclei) in the epidermis. Primary cutaneous Paget disease stains GCDFP-15 positive, CK7 positive, and CK20 negative, while EMPD from an internal malignancy is GCDFP-15 negative, CK7 negative, and CK20 positive.
  - Surgical excision remains the gold standard treatment for EMPD, but Mohs surgery is an emerging treatment that appears to have lower recurrence rates.
  - EMPD differentials include contact dermatitis, psoriasis, seborrheic dermatitis, anogenital intraepithelial neoplasia, lichen sclerosus, and melanoma.

- EMPD lesions recur in approximately 20-30% of cases because the disease is multifocal and often extends beyond clinically apparent areas. Therefore, patients require frequent follow-up and assessment for recurrence.

- 10-30% of EMPD cases are associated with internal malignancies of the bladder, rectum, cervix, prostate, or urethra. Thus, patients with EMPD should be thoroughly investigated to rule out any underlying malignancy.

- To our knowledge, there have been no reports in the literature of development of EMPD in a patient with MF.

Teaching Points

- MF and EMPD are each associated with an increased risk of secondary malignancies, and patients should be evaluated based on signs and symptoms in addition to age-appropriate screenings to rule out any underlying malignancy.
- EMPD should be considered as a differential diagnosis in patients with CTCL who present with pruritic, erythematous, well-demarcated scaly plaques.
- Histopathology and staining can help to distinguish primary vs secondary EMPD.

References:
CASE 14
A 71-YEAR-OLD WOMAN WITH FACIAL PAPULES AND PLAQUES

Patient

MM is a 71-year-old woman.

Presenters

Noah Miranda, MSII
Heather Gochnauer, MD
Fnu Nutan, MD

History

A 71-year-old female presented to her primary care provider with an 18-month history of a pink, pruritic rash on the left cheek. The intense itching woke her from sleep. Following no improvement with topical hydrocortisone, Kenalog injections, and oral antibiotics from two previous providers, she presented to dermatology clinic. Demodex infestation was suspected, and patient completed a course of oral ivermectin and topical selenium sulfide. Over the course of about six months, she failed treatment with doxycycline, fexofenadine, topical clindamycin, metronidazole, azelaic acid, and pimecrolimus. A prior biopsy from an outside provider showed pseudolymphoma, but given no improvement, a repeat biopsy was obtained. Histopathology indicated nonspecific deep lymphohistiocytic infiltrate with eosinophils. Phototherapy was attempted and soon discontinued due to redness and burning. Topical tacrolimus and oral hydroxychloroquine were then initiated for potential pseudolymphoma secondary to contact dermatitis. Patient underwent patch testing, which was negative. Given continued rash and lack of improvement, another biopsy was obtained as well as additional laboratory studies.

Past Medical History: COPD, hypertension, allergic rhinitis, asthma, hypothyroidism, hyperlipidemia

Family History: Brother with lung cancer, coronary artery disease and unspecified heart disease; father with a history of aneurysm; mother with congestive heart failure

Allergies: Trimethoprim-sulfamethoxazole, codeine, morphine, oxycodone-acetaminophen, magnesium salicylate, hydrocodone-acetaminophen, walnut

Medications: Albuterol, rabeprazole, clopidogrel, verapamil SR, montelukast, bupropion, prednisone 10 mg, hydroxychloroquine 200 mg, fexofenadine, atorvastatin, levothyroxine

Physical Examination

On the upper cheeks and lateral face are edematous, pink to red papules and plaques with a small amount of overlying scale.

Laboratory Data

- IgG subclass 4: 606.6 mg/dL (elevated)
- IgG serum: 1662 mg/dL (elevated)
- Serum protein electrophoresis
  - Albumin: 3.7 g/dL (low)
  - Beta 2 globulin: 0.6 g/dL (elevated)
- Urine protein electrophoresis (normal)
- CBC with differential (normal)

Histopathology

Punch biopsy from the left cheek displayed a superficial and deep perivascular and nodular mixed infiltrate composed of lymphocytes, histiocytes, plasma cells, and eosinophils. Inflammation approximates but does not infiltrate the adnexal structures. The epidermis is uninvolved. The infiltrate was further characterized to show CD3 positive T cells with an increased CD4/CD8 ratio, retaining CD5 and CD7. Additionally, there was a small, dispersed population of CD20 B cells as well as abundant plasma cells, without light chain restriction. Notably, the IgG4/IgG ratio was abnormally elevated, with ~60% of plasma cells positive for IgG4 (normal ratio less than 40%). T cell clonality studies were negative.

Treatment

- Oral prednisone taper starting at 30 mg
- Vitamin D and calcium daily supplementation
- Hydroxychloroquine 200 mg daily
CASE 14
A 71-YEAR-OLD WOMAN WITH FACIAL PAPULES AND PLAQUES

**Figure:** (A) Pink plaques on right cheek, dorsal nose and left cheek. (B) Blue circle indicates biopsy site. (C) and (D): Punch biopsy from the left cheek shows a superficial and deep perivascular and nodular mixed infiltrate composed of lymphocytes, histiocytes, plasma cells, and eosinophils. (E) and (F): Notably, the IgG4/IgG ratio was abnormally elevated, with ~60% of plasma cells positive for IgG4 (normal ratio less than 40%).
IgG4-RELATED DISEASE

Discussion

- Epidemiologic studies of IgG4-related disease remain limited since its first description in the early 2000s. A 2019 study estimates an incidence of 5.3 per 100,000 people in the United States.
- IgG4-RD is an immune-mediated condition with a variety of manifestations due to potential involvement of nearly any organ system.
- Clinical phenotypes have been grouped into four distinct categories including pancreato-hepato-biliary, retroperitoneal fibrosis and/or aortitis, classic Mikulicz syndrome with systemic involvement, and head and neck-limited disease.
  - Head and neck limited disease, as suspected in our patient, often presents with chronic enlargement of both salivary glands and lacrimal glands. Patients may also develop orbital swelling and myositis.
- Diagnosis is made by combining clinical manifestations with serum IgG4 and complement levels as well as biopsy or imaging of any masses.
- Biopsy and serum results could show activated B-cells, T-cells (CD3+) and plasma cells with greater than 40% of all IgG over-expression being IgG4. Of note, not all patients with inclusionary biopsy will have over-expression of IgG4 in serum.
- Major histopathological features include dense lymphoplasmacytic infiltrate, characteristic storiform fibrosis, and obliterator phlebitis. Increased numbers of eosinophils are often seen, but cannot alone make the diagnosis.
- First line treatment is glucocorticoids, often 30-40 mg daily prednisone, for approximately 2-4 weeks. This should be followed by a gradual taper over 3-6 months.
- Disease often flares during or after glucocorticoid taper and steroid-sparing agents are needed, such as cyclophosphamide or mycophenolate mofetil. Rituximab has shown promising efficacy as an initial treatment option and maintenance therapy.
- Studies have not shown an increased risk of malignancy in patients with IgG4-RD. However, as a relatively new diagnosis, long-term, quantitative prognostic data is lacking. For those with pancreato-hepato-biliary or aortitis, treatment is critical as untreated patients have a higher morbidity and mortality.

Teaching Points

- Include IgG4-related disease on the differential diagnosis for refractory head and neck rashes.
- Although there is a current lack of data and official guidance regarding malignancy risk in patients with IgG4-RD, patients should be monitored for concurrent or distinct malignancies.
- Histopathology is the key to diagnosis. Important pathology features of IgG4-RD are mild to moderate eosinophil infiltration, storiform fibrosis as well as an elevated number of IgG4+ plasma cells within tissue. A lymphoproliferative disorder must be excluded.

References:

CASE 15

A 76-YEAR-OLD WOMAN WITH RETIFORM PURPURA OF THE BILATERAL LOWER EXTREMITIES FOLLOWING INTRALESIONAL 5-FU

Patient

KG is a 76-year-old woman.

Presenters

Elaine Flynn, Research Year/MSIV
Haley Neff, MSII
Kelly Flanagan, MD
Mark Scharf, MD

History

A 77-year-old woman with end-stage renal disease on dialysis awaiting kidney transplantation, capillaritis of her bilateral lower extremities, and multiple prior keratinocyte carcinomas, presented with purple discoloration of her shins. She had received treatment for multiple squamous cell carcinomas of the lower legs with 3 doses of intralesional 50mg/ml 5% 5-fluorouracil (5-FU), given over a 5-month period. The last injection was given 3 months prior to the patient’s presentation for shin discoloration. The patient reported that the discoloration had intensified over the last few months.

Past Medical History: End-stage renal disease (ESRD) secondary to hypertension and solitary kidney, numerous prior squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs), Hashimoto’s thyroiditis, hypertrophic obstructive cardiomyopathy, secondary hyperparathyroidism, tubular adenoma of the colon, triple negative invasive ductal carcinoma of the breast s/p radiation

Family History: None

Allergies: Iodinated contrast media, iodine, ACE inhibitors, indomethacin, sulfonamide antibiotics

Medications: Atorvastatin, cinacalcet, levothyroxine, miconazole 2% powder, midodrine, tretinoin 0.1% cream, urea 40% cream

Physical Examination

Purpuric reticular plaques across the bilateral anterior lower legs, extending from just above ankles to just below knees

Laboratory Data

- RBC 3.15 10⁶/uL (low)
- Hemoglobin 11.4 g/dL (low)
- Platelets 128 10³/uL (low)
- Creatinine 7.8 (elevated)
- TSH 26.127 uIU/mL (elevated)
- Free T4 0.79 ng/dL (normal)

Histopathology

Punch biopsy of left superomedial lower leg demonstrated superficial dermal hemorrhage and scar with hemosiderin deposition. No intravascular thrombi or vasculitis was seen. Direct immunofluorescence was negative.

Treatment

Current treatments:
- Daily compression stockings
- Emollients

Previous treatments:
- Topicals: Tretinoin 0.1% cream, alclometasone 0.05% cream without significant improvement
- Test doses of pulsed dye laser without significant improvement
CASE 15
A 76-YEAR-OLD WOMAN WITH RETIFORM PURPURA OF THE BILATERAL LOWER EXTREMITIES FOLLOWING INTRALESIONAL 5-FU

Figure: (A) Purpuric reticular plaques on bilateral anterior lower legs, extending from just above ankles to just below knees. (B) Closer up photograph of reticular plaques on left superior lower leg with punch biopsy sites. (C) and (D): Punch biopsy of left medial leg demonstrating superficial dermal hemorrhage with scar, superficial and deep hemosiderin deposits, and focal lipomembranous change, overall consistent with purpura on background of chronic stasis changes.
RETIFORM PURPURA FOLLOWING 5-FU INTRALESIONAL INJECTIONS FOR NMSC

Discussion

- Retiform purpura are hemorrhagic lesions with an angulated configuration caused by cutaneous ischemia secondary to compromised vasculature. Numerous diseases may manifest as retiform purpura.
- Pathophysiology involves vascular occlusion and damage to cutaneous blood vessels. Several disease processes involving embolization, thrombosis, protein deposition and certain opportunistic infections in immunocompromised hosts are associated with retiform purpura.
- Of note, the distribution of retiform purpura may offer clues to the diagnosis. Lower extremity lesions, as seen in this patient, are associated with vasculitis, cholesterol emboli, and livedoid vasculopathy, while lesions favoring adipose rich tissue such as the buttocks and thighs are associated with heparin or warfarin-induced skin necrosis and calciphylaxis.
- In this patient, 5-fluorouracil (5-FU) intralesional injections for multiple keratinocyte carcinomas on the lower legs preceded development of retiform purpura in the treated area. Histopathology did not support any inflammatory, embolic or thrombotic causes of retiform purpura. We are concerned for reactive retiform purpura to 5-FU, which potentially induced a severe capillaritis due to extensive actinic damage of lower legs.
- 5-FU is a chemotherapeutic agent that functions as an antimetabolite by competitively inhibiting thymidylate synthase. It has been safe and effective when used topically for the treatment of Bowen’s disease, warts, and actinic keratosis. Though surgical excision is the gold standard treatment for cutaneous SCC (cSCC), intralesional 5-FU has been used to treat SCC when the location of the lesion (eg. lower limb), patient age, and co-morbidities such as diabetes, increase the risk of surgical complications of bleeding, dehiscence, infection, and non-healing.
- Purpura has been reported as an adverse effect associated with intralesional 5-FU in the treatment of oculofacial keloidal and hypertrophic scars. Literature has also demonstrated risk of hyperpigmentation following intralesional 5-FU. To our knowledge, retiform purpura has not previously been reported as an adverse even of intralesional 5-FU.

Teaching Points

- Life threatening presentations of retiform purpura such as disseminated intravascular coagulation (DIC), bacterial sepsis, warfarin skin necrosis and purpura fulminans must be promptly identified and managed.
- Reported adverse effects of intralesional 5-FU in the treatment of cSCC are usually self-limited injection site reactions such as purpura, site discoloration, hyperpigmentation, local pruritus, erythema, scaling, and tenderness.
- Herein, we present a case of chronic retiform purpura following multiple 5-FU injections, which potentially induced a severe capillaritis with resulting hemorrhage due to extensive actinic damage of lower legs.

References:
**CASE 16**

**A 22-YEAR-OLD MAN WITH THICKENED SKIN OF HIS BILATERAL HANDS AND FEET**

**Patient**

XT is a 22-year-old man.

**Presenters**

Beatriz Fernandes, MSIII  
Maggi Ahmed, MD, PhD  
Isabella Plumptre, MBBS  
Karen Wiss, MD

**History**

A 22-year-old man with a desmoplakin (DSP) mutation presented with painful thickened skin of his bilateral hands and feet since childhood. He described significant discomfort when walking or running, pruritus of the thickened skin, and thickened discolored fingernails and toenails. Multiple topical treatments had been tried without improvement, including urea cream, salicylic acid, oatmeal soaks, Epsom salt soaks, and topical steroids.

The patient also noted bumps on the scalp previously diagnosed as dissecting cellulitis. He had partial improvement after two years of therapy with topical clindamycin, oral minocycline and rifampin by his referring dermatologist. He was switched from minocycline to doxycycline given the improved safety profile. Isotretinoin was deferred given concern for increased risk of cardiomyopathy from the patient’s cardiologist.

**Past Medical History:** GERD, ADHD, migraine

**Family History:** Father and half-brother with known DSP gene mutation, keratoderma, woolly hair, and cardiomyopathy requiring implantable cardioverter defibrillators. His half-brother, who was presented at a previous NEDS meeting, had significant improvement of skin involvement since starting ustekinumab.

**Allergies:** Azithromycin (urticaria)

**Medications:** Doxycycline, rifampin, clindamycin 1% solution, butalbital-acetaminophen-caffeine

**Physical Examination**

**Skin:**
- Hyperkeratotic plaques on the palmoplantar surfaces and a few scattered keratotic papules over dorsal MCPs of the bilateral hands
- Fingernails: thickened with leukonychia, onychoschizia and horizontal bandlike accentuations
- Toenails: Thickened with onycholysis.
- Temporal/occipital scalp: Scalp hair is tightly coiled, with several pink tender papules, pustules, and cysts. No scaling noted.

**HEENT:** No teeth anomalies noted

**Laboratory Data**

- Desmoplakin (DSP) gene mutation, C.1790C>T p.Ser597Leu, heterozygous
- Quantiferon Gold negative
- Viral hepatitis panel negative

**Treatment**

- Ustekinumab 45 mg subcutaneous injection on week 0, 4, then every 12 weeks – approved but not yet started
- Rifampin 300 mg and doxycycline 100 mg BID with plan to taper once on ustekinumab
- Clindamycin 1% solution BID
- Calcipotriene 0.005% cream BID
CASE 16
A 22-YEAR-OLD MAN WITH THICKNED SKIN OF HIS BILATERAL HANDS AND FEET

Figure: (A) Keratotic papules overlying the dorsal MCPs with thickened fingernails and leukonychia. (B) Keratotic plaques on palmar surfaces of the bilateral hands. (C) Hyperkeratosis of the dorsal feet with leukonychia and mild onycholysis of toenails. (D) Occipital scalp with tight coiled hair strands on a mildly erythematous and scarred background.
DILATED CARDIOMYOPATHY WITH WOOLLY HAIR, KERATODERMA, AND TOOTH AGENESIS

Discussion

- Dilated Cardiomyopathy with Woolly Hair, Keratoderma, and Tooth Agenesis (DCWHKTA) is a rare, autosomal dominant genetic disorder caused by loss of function mutations in the desmoplakin gene (DSP). Desmoplakin is a desmosomal protein involved in intracellular tight junctions. Given the critical role of tight junctions in cardiac tissue, patients with DCWHKTA are at high risk of developing dilated cardiomyopathy.
- DCWHKTA presents with palmoplantar keratoderma, tightly coiled ‘woolly’ hair, thickened nails, and teeth anomalies. There is variable expressivity of the cutaneous findings. Cutaneous findings often precede cardiac complications. The cardiac manifestations of arrhythmogenic cardiomyopathy are often asymptomatic, and can lead to sudden death.
- The management of DCWHKTA includes:
  - Cardiac: implantable cardioverter-defibrillator placement, medical therapy for congestive heart failure
  - Dermatologic: soaks, emollients, paring, topical keratolytics, topical and systemic retinoids
- DCWHKTA differs from autosomal recessive cardiocutaneous syndromes like Naxos disease (type I keratoderma) and Carvajal disease (type II keratoderma). Naxos and Carvajal disease present with a triad of woolly hair, palmoplantar keratoderma, and cardiomyopathy (classically arrhythmogenic right ventricular cardiomyopathy in Naxos, versus dilated left ventricular cardiomyopathy in Carvajal).

Teaching Points

- Cardiac involvement in DCWHKTA is often asymptomatic in the early stages. Cutaneous and hair findings may be the first presenting features.
- The combination of “woolly” hair and palmoplantar keratoderma (+/- dental abnormalities and nail dystrophy) should prompt referral to genetics and cardiology for diagnostic workup and early life-saving cardiac interventions.
- Off-label use of ustekinumab has been shown to improve symptoms of PPK in a published case series.

References:
CASE 17
A 23 MONTH-OLD MALE WITH BROWN, PLATE-LIKE SCALE, ECTROPIUM AND ECLABIUM

Patient
VS is a 23-month-old male.

Presenters
Jessica Orofino, MSII
Holly Neale, MD
Karen Wiss, MD

History
A 23-month-old male presented initially at 12 days of life for skin peeling and brown, plate-like scale. At birth, collodion membrane, diffuse peeling, crease fissures, ectropion, and eclabium with underlying erythema were present. Collodion covered the ears; he has since developed moderate ear canal obstruction by sloughing skin and is followed by pediatric otolaryngology for conductive hearing loss. He experienced three episodes of temperature dysregulation in the first six months of life (requiring NICU admission at age 15 days) and developed a MRSA infection of the fifth finger at 18 months. His cutaneous findings have not caused pain. He has normal growth, social skills, feeding, and voiding.

Past Medical History: Born via vaginal delivery at 34w2d. Peri-natal history includes maternal gestational diabetes, PPROM, and transient neonatal respiratory distress. Developed bronchiolitis/pneumonia at ages 10 and 21 months; diagnosed with reactive airway disease. Speech and mild gross motor skill delays observed.

Family History: Father with eczema and scalp psoriasis. Older brother is a carrier of TGM1 mutation.

Allergies: None

Medications: Cholecalciferol, ferrous sulfate

Physical Examination
Skin: Diffuse coarse, brown, plate-like scales with minimal underlying erythema are present over all skin. Scales are thicker on the scalp, hands, and feet, and thinner along the trunk, extremities, and face.

HEENT: Ectropion and eclabium

Laboratory Data
• Genetics confirmed TGM1 mutation.

Treatment
• Skin barrier maintenance: humidifier use, emollient minimum three times daily (Aquaphor ointment, DermaPhor ointment, mineral oil/hydrophilic petrolatum ointment, vegetable glycerin, petroleum jelly and/or virgin coconut oil)
• Scale: daily bath, Neutrogena T-sal shampoo, castor oil and combing of scalp scale
• Thermoregulation: 100% cotton clothing, cool water spritz as needed on hot days
• Infection risk: mupirocin 2% ointment to the nares for 10 days/month (plus family members), bleach baths, avoidance of skin trauma (use nail file instead of clippers)
• Developmental: Early Intervention for speech delay and mild gross motor delay
• Eyes: managed by ophthalmology with carboxymethylcellulose 1% ophthalmic solution and hypromellose 0.3% gel ophthalmic gel for ocular lubrication, and polymyxin B sulf-trimethoprim ophthalmic solution for infection
• Ears: managed by otolaryngology with acetic acid 2% otic solution used twice daily, ear cleanings every 6 weeks, and hearing aid
CASE 17
A 23 MONTH-OLD MALE WITH BROWN, PLATE-LIKE SCALE, ECTROPIUM AND ECLABIUM

Figure: (A) At 2 months of age, diffuse brown, plate-like scale is evident. (B) Age 5 months, ectropion and brown plate-like scale of the scalp are present. (C) At age 21 months there is generalized scaling. (D) Age 21 months, there is persistent ectropion and scalp hair growth.
LAMELLAR ICHTHYOSIS WITH TGM1 MUTATION

Discussion

- Lamellar ichthyosis (LI) is a rare, inherited condition resulting in disrupted cornification of the epidermis, which can present with varying severity starting within the first few weeks of life. Over time, LI classically presents with thick, hyperkeratotic dark scales covering a majority of the body; the largest and darkest scales typically overly the lower extremities. There can be varying degrees of inflammation.
- It has been estimated that fewer than 5000 people in the United States have LI, and it is typically inherited in an autosomal recessive manner, with 80-90% of cases arising from a TGM1 mutation. TGM1 mutations are present in 26.9% of autosomal recessive ichthyoses overall.
- TGM1 encodes the enzyme transglutaminase 1, responsible for esterification and cross-linking proteins necessary to form the cornified cell envelope that helps maintain skin hydration. The disrupted moisture barrier can contribute to transepidermal water loss and subsequent dehydration. Scale formation in LI can additionally disrupt sweat glands, impairing thermoregulation.
- Findings associated more commonly with TGM1 mutations include: presence of collodion membrane at birth, skin odor, hearing complications, eye complications, and alopecia.
- Ectropion is present in 80-90% of TGM1 LI. Lifelong close ophthalmology follow up is critical to prevent complications such as corneal erosions, infection, and blindness.
- Ear involvement can lead to conductive hearing loss from debris accumulating in the ear canal.
- Systemic retinoids are reserved for patients with more severe forms of LI and should be given at the lowest effective dose (1 mg/kg/day or less). Capsules can be chewed and for infants, the contents can be added to food, breast milk, or formula after poking a hole in the tough capsule. Systemic retinoids in children may cause premature epiphyseal closure, tendon/ligament ossifications, bone spurs, and cardiovascular complications.

Teaching Points

- LI due to TGM1 mutation is a rare, chronic, autosomal recessive genetic disorder that presents with collodion membrane at birth and dark, plate-like scales which can cover much of the body.
- The gold standard of diagnosis is genetic testing.
- Cutaneous manifestations of LI are commonly treated with liberal topical emollients, humidity of the environment, and frequent bathing. Products containing lactic acid, glycolic acid, or alcohol should be avoided due to risk of systemic absorption.
- Diagnosis and management require a multidisciplinary care approach involving pediatrics, genetics, dermatology, ophthalmology, and otolaryngology.

References:

CASE 18A
A 41-YEAR-OLD MALE WITH A BLISTERING FACIAL RASH

Patient
AM is a 41-year-old male.

Presenters
Stephanie Choi, MSIII
Amina Tariq, MSII
Lindsay McCormack, MD
Fnu Nutan, MD

History
A 41-year-old male originally from Puerto Rico presented to the ED with progressively worsening pruritic, yellow crusted plaques on the face and right foot. This eruption began one month prior, predominantly on the right foot. He presented to the ED at that time and was treated for right foot “cellulitis” with oral clindamycin, morphine, and Toradol. Shortly after, he noted several “blisters” over the glabella; these gradually enlarged and became increasingly pruritic with associated yellow fluid drainage and a burning sensation. Lesions then spread to most of the face and chest with associated periorbital edema. Lesions on the right foot continued to develop worsening erosions and thickly crusted plaques. He denied systemic symptoms, including fever, chills, fatigue, headache, vision or hearing changes, or abdominal complaints.

Past Medical History: Alcohol use disorder, nicotine dependence (58 pack-year history)

Family History: Noncontributory

Allergies: None

Medications: Clindamycin 150 mg PO TID, morphine 4 mg PO once, and ketorolac 15 mg IV once were given for right foot “cellulitis” one month prior to presentation.

Physical Examination
General: Visibly uncomfortable but pleasant mood.
Skin: Full facial edema was noted, most pronounced in the periorbital region. Pink-red erythematous weeping plaques with thick yellow adherent crust were present over the glabella, forehead, bilateral frontal and temporal scalp, and less prominently on bilateral temples, perinasal cheeks, and the beard distribution. Many clustered small yellow and hemorrhagic vesicles were present on the temples, periauricular cheeks, and postauricular scalp. Right foot showed skin erosions and thickly crusted plaques, more prominent on the plantar surface.

Laboratory Data
- WBC 13,300/µL (elevated); Absolute eosinophil count 1200/µL (elevated)
- Skin culture positive for methicillin-resistant Staphylococcus aureus and Acinetobacter pittii

Histopathology
Punch biopsy for H&E from the right lateral neck revealed loss of the stratum corneum and granular cell layer with background spongiotic dermatitis and eosinophils. Direct immunofluorescence for intercellular IgG and IgA were weakly positive. Direct immunofluorescence was negative for IgM, C3, and fibrinogen.

Treatment
- Prednisone 60 mg PO once daily was started until follow-up with dermatology 1 to 2 weeks after discharge.
- Hydrocortisone 2.5% ointment BID to all affected regions of the face and body.
- Fluocinonide 0.05% solution BID to the scalp.
- Mupirocin ointment BID to eroded regions.
- Initially, mycophenolate mofetil 1 gram PO BID was planned to start at follow-up. However, this was not initiated as symptoms resolved and did not recur.
CASE 18A
A 41-YEAR-OLD MALE WITH A BLISTERING FACIAL RASH

**Figure:** (A) Pink-red erythematous weepy plaques with thick yellow adherent crust over the glabella, forehead, and bilateral frontal scalp. (B) Clustered vesicles with yellow and hemorrhagic fluid on the left temple and periauricular cheeks. (C) Biopsy demonstrating loss of stratum corneum and granular cell layer with a background of spongiotic dermatitis and eosinophils. (D) DIF positive for IgG.
CASE 18B
A 12-YEAR-OLD MALE WITH PRURITIC, RED, SCALY PLAQUES ON THE FACE, TRUNK, AND EXTREMITIES

Patient
BP is a 12-year-old male.

Presenters
Christine Li, MSIII
Heather Gochnauer, MD
Leah Belazarian, MD

History
An otherwise healthy 12-year-old boy developed an erythematous, pruritic lesion on his arm. Over the course of a month, pruritic, scaly lesions appeared on his face, scalp, trunk, arms, and legs. He was prescribed topical hydrocortisone cream and cephalaxin without effect. One week prior to his dermatology appointment, he presented to the Emergency Department (ED) with worsening pruritus, and now painful plaques with yellow and hemorrhagic crusting. Culture was positive for *S. aureus*, and he was started on topical mupirocin, oral clindamycin, and oral cetirizine without improvement. He then presented to dermatology clinic. Two biopsies were obtained.

Past Medical History: None
Family History: Noncontributory
Allergies: None
Medications: Cetirizine, oral clindamycin, mupirocin ointment

Physical Examination
Widespread shallow erosions and excoriations were seen on the face, scalp, trunk, arms, legs, with sparing of the mucous membranes, fingers, feet, and groin; some with overlying hemorrhagic crust or peripheral white collarette of scale. Several scaly papules and plaques were present on the central chest and arms.

Histopathology
Punch biopsy from the left upper arm displayed epidermal acantholysis at the level of the granular layer. Direct immunofluorescence was positive for intercellular IgG and C3.

Treatment
- Initially treated with 18-day oral prednisone taper starting at 50 mg daily and triamcinolone 0.1% ointment, with some improvement. Added fluocinolone 0.01% solution for scalp and desonide 0.05% ointment for thighs.
- Three weeks after initial dermatology visit, he presented to the ED with worsening pain associated with nonhealing existing lesions, worse over posterior thighs. Endorsed 1 day of subjective fever, nausea, and vomiting. Exam revealed scattered large erosions involving >40% of BSA. Some flaccid vesicles overlying thighs were noted as well as hyperpigmented-to-red macules and patches. Given high BSA involvement and concern for impending exfoliative erythroderma, patient was admitted for 3 days. He was treated with a 2-day course of IVIG 0.75 g/kg/day and started on oral prednisone 50 mg (1 mg/kg/day). He was discharged on oral prednisone 50 mg, hydrocortisone 1% ointment for face, and triamcinolone 0.5% ointment for body with great improvement.
- One month after discharge, he was transitioned to dapsone 75 mg (1.5 mg/kg/day), fluocinolone 0.05% solution for scalp, and triamcinolone 0.1% ointment for body, with significant improvement although not completely clear.
- Currently managed on dapsone 100 mg (2 mg/kg/day), fluocinonide 0.05% solution for scalp, alclometasone 0.05% ointment for face, and mometasone 0.1% ointment for body, with regular CBC and CMP monitoring.
CASE 18B
A 12-YEAR-OLD MALE WITH PRURITIC, RED, SCALY PLAQUES ON THE FACE, TRUNK, AND EXTREMITIES

Figure 1: Initial dermatology evaluation of lesions with hemorrhagic and yellow crust involving the face and scalp (A), chest (B), back, and extremities. Three weeks later, the patient was admitted for persistent lesions (C, D) accompanied by worsening pain and drainage, especially over the posterior thighs.

Figure 2: One week after discharge, patient presented for outpatient follow-up with lesions at various stages of healing involving the face and scalp (A), chest, back (B), and extremities (C, D).

Figure 3: (A) Punch biopsy from the left upper arm displayed epidermal acantholysis at the level of the granular layer. (B) Direct immunofluorescence was positive for intercellular IgG (shown) and C3.
PEMPHIGUS FOLIACEUS

Discussion

- Pemphigus foliaceus (PF) is an acquired, potentially life-threatening autoimmune disease characterized by superficial blisters of the skin and IgG autoantibodies against desmoglein-1.
- PF most commonly occurs in adults between 50 to 60 years of age. Pediatric PF is rare, with only ~33 reported cases in the literature to date (57.6% male and 42.4% female, mean age of 10.6 years). Prognosis is more favorable among children compared to adults but may still be fatal if left untreated.
- Pediatric and adult PF present similarly, with scattered, flaccid, superficial vesicles and bullae that rapidly evolve into scaly, crusted erosions. PF often initially involves the seborrheic regions of the face and scalp, before progressing to the trunk and extremities. PF may remain localized or quickly coalesce to involve large areas of skin, resulting in exfoliative erythroderma. Nikolsky sign is usually present. PF typically spares the mucous membranes (unlike pemphigus vulgaris (PV)) given high levels of desmoglein-3 and relatively low levels of desmoglein-1 expressed in mucosa). The palmoplantar surfaces are also spared.
- Diagnosis is by biopsy of an early skin lesion for H&E staining and of adjacent perilesional unaffected skin for DIF. Characteristic H&E findings include acantholysis and mixed inflammatory infiltrate in the superficial dermis. DIF shows deposition of intercellular IgG and C3 throughout the epidermis, as seen in PV, although some cases of PF may demonstrate IgG restricted to the upper epidermal layers. Other diagnostic tools include indirect immunofluorescence and ELISA.
- Systemic steroid therapy (1 to 2 mg/kg/day) ± nonsteroidal adjunctive agents (i.e., dapsone up to 1.5 mg/kg/day) is considered first line for pediatric and mild adult PF, with expected clinical improvement in 2 to 3 weeks. Other common adjunctive agents include azathioprine (1 to 3 mg/kg/day) and mycophenolate (2 g/day).
  - Moderate to severe adult PF should be treated with systemic steroids and rituximab as first line agents.
  - Severe or refractory cases may benefit from intravenous immune globulin (IVIG) (2 g/kg/cycle over 2 to 5 days at 4-to-6-week intervals) ± rituximab (using the lymphoma or rheumatoid arthritis protocol).
  - Only two cases of IVIG-treated pediatric PF have been reported in the literature. Both had severe, generalized involvement refractory to corticosteroids ± immunosuppressants, and IVIG was started in combination with oral steroids, as in our patient. While our patient exhibited clinical improvement with IVIG, the two reported cases required additional treatment with rituximab monotherapy or combination therapy with IVIG and rituximab to achieve disease control.

Teaching Points

- PF can have a subtle initial onset; only the resultant crust and scale may be evident, as the superficial blisters are easily ruptured and may not be seen at the time of presentation.
- IVIG can be a useful treatment either as monotherapy or as combination therapy, as seen in our pediatric patient.
- Mild PF in adults may be treated with dapsone, but recent consensus expert guidelines recommend rituximab as a first line agent.
- Relapses are common in PF patients once they are off systemic steroids. Ideally, they should be started on steroid sparing agents like azathioprine or mycophenolate along with systemic steroids. Pediatric patients may be especially susceptible to PF exacerbations from sun exposure.

References:
CASE 19
AN 8-YEAR-OLD GIRL WITH GENERALIZED AND LINEAR DISTRIBUTION OF SCALY, ERYTHEMATOUS, PRURITIC PLAQUES

Patient
AV is an 8-year-old girl.

Presenters
Michael Frisoli, PhD, MSIII
Kelly Flanagan, MD
Leah Belazarian, MD

History
An 8-year-old previously healthy girl with recent sore throat (no bacterial culture available) developed a widespread pink, scaly, itchy skin eruption. Most of her body was involved, including the abdomen, back, right arm, right leg, forehead, and scalp. With time, the plaques thickened and developed significant white scale. Her right foot was also significantly affected with itchy and painful plaques, which made it difficult for her to walk.

Prior to presentation to dermatology, lesions did not improve with topical treatment, including triamcinolone 0.1% ointment and hydrocortisone 2.5% cream. She had also seen podiatry and was treated for right great toe onychomycosis with oral terbinafine without improvement.

Past Medical History: None
Family History: Noncontributory
Allergies: None
Medications: Triamcinolone 0.1% ointment BID, hydrocortisone 2.5% cream BID, terbinafine 125 mg PO daily for ~1 month

Physical Examination
Extending from the right groin to the right great toe, there are thin pink plaques distributed in a blaschkoid pattern. There is a circumferential pink, scaly plaque on the right great toe with a dystrophic toenail. A thin scaly, light pink plaque is also present on the medial sole of the right foot.

Thin plaques, some with micaceous scale, are present on the scalp and postauricular areas, and are scattered on abdomen, back and right arm. Fingernails have areas of pitting.

Laboratory Data
• WBC 7.1 10^3/µl (normal)

Histopathology
Punch biopsies from the right leg and upper back both showed psoriasiform epidermal hyperplasia and mild spongiosis with atypical lymphocytic infiltrates. Infiltrates were predominantly CD3+ with reversed CD4:CD8 ratio (1:4) and reduced CD7 expression. PCR analysis of T cell receptor gamma chain (TRG) rearrangement to detect oligoclonal expansion of gamma delta T cells was negative.

Treatment
• Topical treatments: fluorocinonide 0.05% cream nightly (postauricular), calcipotriene 0.05% ointment BID (face), mometasone 0.1% ointment BID (body), betamethasone 0.05% ointment BID (tapered with improvement, right foot), ketoconazole 2% shampoo
• Ustekinumab (July 2022 – January 2023) with minimal improvement
• Ixekizumab (February 2023 – current)
• Methotrexate 15 mg weekly with folic acid 1 mg daily (December 2023 – current)
CASE 19

AN 8-YEAR-OLD GIRL WITH GENERALIZED AND LINEAR DISTRIBUTION OF SCALY, ERYTHEMATOUS, PRURITIC PLAQUES

Figure: (A) Scattered pink plaques on the patient’s back. (B)-(D): Pink and hypopigmented plaques and patches in blaschkoid pattern extending from right groin to right great toe with associated nail dystrophy. (E) Scaly pink plaque extends to right sole of foot. (F) Punch biopsies from the upper back and right leg displayed psoriasiform hyperplasia with mild spongiosis and a brisk superficial lymphocytic infiltrate with minimal cytological atypia and exocytosis. The lymphocytic infiltrate was CD3 positive, CD8 predominant with reduced CD7 expression. TCR gene rearrangement was negative for clonality, favoring a reactive process.
SUPERIMPOSED LINEAR PSORIASIS

Discussion

- Genetic mosaicism resulting from loss of heterozygosity within epidermal cells can cause polygenic skin diseases to present as isolated segmental lesions, or as superimposed segmental lesions in the setting of generalized skin disease. Mosaicism of keratinocytes can manifest as skin findings that follow Blaschko lines.
- Dr. Happle published a series of case reports of superimposed segmental lesions presenting in numerous generalized inflammatory skin diseases, including psoriasis, pustular psoriasis, atopic dermatitis, lichen planus, vitiligo, systemic lupus erythematosus, and pemphigus vulgaris. Relative to generalized lesions, segmental lesions were generally noted to present sooner, to have a pronounced phenotype, and to be difficult to treat.
- Here, we present a case of generalized with superimposed linear psoriasis, the latter of which was particularly difficult to treat with anti-psoriatic medications. Interestingly, the generalized lesions have responded better than the linear portion—with notable recalcitrant lesions on the great toe and right sole of foot. In contrast to Dr. Happle’s observations, segmental linear lesions on the right leg of this patient did not appear before generalized lesions.
- To date, no mosaic gene mutations have been specifically associated with linear psoriasis, yet a somatic gain of function point mutation in HRAS within keratinocytes has been associated with a case of unilateral psoriasis. A published mouse study also demonstrated that constitutively Raf, a downstream kinase activated by Ras GTPases, within keratinocytes can lead to psoriasis-like skin inflammation.

Teaching Points

- Genetic mosaicism is believed to drive development of segmental inflammatory skin disease, which can present as isolated segmental lesions or as superimposed segmental lesions among widespread disease. It is important to recognize segmental lesions, as they can often be difficult to treat.
- Linear psoriasis may require potent treatments including high strength topical corticosteroids, biologics targeting the IL23-IL17A inflammatory pathway, and/or methotrexate.

References:

CASE 20
AN 8-YEAR-OLD GIRL WITH SKIN BLISTERS SINCE BIRTH

Patient
GVS is an 8-year-old girl.

Presenters
Priscilla Romano, MD
Lindsay McCormack, MD
Diana B. Reusch, MD
Karen Wiss, MD

History
GVS is an 8-year-old female with a history of cutaneous blistering since birth. She received a clinical diagnosis of recessive dystrophic epidermolysis bullosa (RDEB) in Brazil, experiencing widespread erosions on her skin and oral mucosa at sites of trauma. By the age of 2 years, she required multiple hospitalizations for infections, weakness, anemia, and malnutrition.

The patient presented to the UMass Department of Dermatology in 2022 at the age of 6 for consideration in the Abeona EB-101 trial, evaluating safety and efficacy of gene-corrected keratinocyte sheets with C7 expression for the treatment of extensive and persistent RDEB wounds. An initial 6 grafts and 2 controls were placed in February 2022; 8 additional grafts were placed in June 2023. At the most recent follow-up examination at week 24 visit of the Abeona study, following the second graft transplantation, she has had notable improvement in the treated wounds and has not required hospitalization since commencement of the clinical trial in 2022.

Past Medical History: Chronic pain, chronic constipation, dysphagia, iron deficiency anemia, malnutrition, pseudosyndactyly, inability to walk or stand

Family History: Female sibling passed from sepsis at 3 years of age due to RDEB.

Medications: Morphine 4 mg po before dressing changes, gabapentin 200 mg po q8h, acetaminophen 160 mg po daily, iron sulfate 20 mg po daily, omeprazole 20 mg po daily, hydroxyzine 8 mg po q8h, zinc & vitamins A, C and D po daily, eye lubricant nightly
Wound care: Mepitel to open areas, Mepilex transfer and Tubifast to all wounds

Physical Examination
There are multiple ulcers and erosions on the trunk and extremities. BSA for open wounds is approximately 30%. Estimated BSA for all skin findings is approximately 75%. All 20 nails are absent. There are many oral erosions as well as microstomia and ankyloglossia. There is complete fusion of toes and pseudosyndactyly of both hands.

Laboratory Data
- Genetic/Diagnostic testing: Two heterozygous variants were identified in the COL7A1 gene: the chr3:48,584,322 T>TG variant and the chr3:48,571,250 C>T variant
- Wound cultures (A): Pseudomonas aeruginosa, Staphylococcus aureus
- CBC with auto differential: WBC 26.2 10^3/μL (4.5-13.5 10^3/μL), hemoglobin 9.5g/dL (11.5-15.5g/dL), hematocrit 30.9% (35-45%), MCV 62.4 fl (77-95 fl), MCH 19.1 pg (25-33 pg), RDW 19.3% (11-15%), platelets 928 10^3/μL (140-440 10^3/μL)
- CMP: Total protein 9.5 g/dL (6-8 g/dL), albumin 3.0 g/dL (3.2-5.2 g/dL), bilirubin total 0.2 g/dL (0.3-1.2 g/dL), ALT 8 U/L (10-40 U/L), prealbumin 8 mg/dL (18-40 mg/dL)
- CRP 64.5 mg/L (1.0-3.0 mg/L)
- HIV, hepatitis B, and hepatitis C negative
- Transthoracic echo: normal

Treatment
- Daily wound care as above.
- Punch biopsies were obtained in the OR and sent to Abeona Therapeutics, Inc. for processing, keratinocyte isolation with functional CO7A1 gene transfer, expansion, and production of gene-corrected epidermal sheets.
- 14 autologous gene-corrected skin grafts were surgically transplanted onto the most severe wounds.
CASE 20
AN 8-YEAR-OLD GIRL WITH SKIN BLISTERS SINCE BIRTH

**Figure 1:** Clinical assessment before and after 1st surgical transplantation on left medial upper back. February 2022. (A) Screening visit. (B) Graft Transplantation. (C) Week 12 Post-op. (D) Week 24 Post-Op

A1 Control/A2 Treated

**Figure 2:** Clinical assessment before and after 2nd surgical transplantation on right posterior hip. June 2023. (A) Screening visit. (B) Graft Transplantation. (C) Week 12 Post-op. (D) Week 24 Post-op
CASE 20
AN 8-YEAR-OLD GIRL WITH SKIN BLISTERS SINCE BIRTH

Figure 3: EB-101 Treatment Process. Abeona Therapeutics Inc.
GENE-CORRECTED KERATINOCYTE TRANSFER FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSAA

Discussion

- Epidermolysis bullosa (EB) includes a group of rare, inherited disorders characterized by marked mechanical fragility of epithelial tissues, with blistering and erosions following minor trauma. Four major types of EB are recognized: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler syndrome (KS).
- Dystrophic epidermolysis bullosa is caused by damaging variants in COL7A1, which lead to a complete lack or dysfunction of its encoded type VII collagen (C7). The C7 protein is the major component of anchoring fibrils responsible for the binding of the epidermis and dermis.
- Treatment for RDEB patients is historically supportive and requires a patient-centric multidisciplinary approach for the effective management of these individuals, including wound care, control of infection, nutritional support, and management of additional complications.
- There are two new FDA-approved treatments for dystrophic EB. Vyjuvek (May 2023) is a topical gel that utilizes HSV-1 vector to deliver COL7A1. Filsuvez (December 2023) is a topical gel derived from birch triterpenes.
- This case presents the use of autologous genetically-corrected skin grafts (Abeona EB-101) as treatment for an 8-year-old girl with RDEB. In this case, EB-101 led to rapid closure of large wound areas, promoted faster healing, reduced infections and hospitalizations, and improved quality of life. The product is anticipated to have FDA approval in May 2024 with the key findings of sustained wound healing response and safety data up to 8 years.

Teaching Points

- Historical management approaches for RDEB were mostly palliative; however, novel therapies are emerging.
- Gene-corrected skin graft transplantation is well-tolerated and may be effective in promoting long-term wound healing for patients with RDEB.
- Improved wound healing due to novel therapies may prevent serious complications of RDEB, decrease hospitalizations, and improve quality of life.

References:

CASE 21
A 23-YEAR-OLD MAN WITH RECURRENT BLISTERS AND NAIL DYSTROPHY

**Patient**
LM is a 23-year-old male.

**Presenters**
Robert Li, MSIII
Chris Mahir, MSIII
Sarah Servattalab, MD
Karen Wiss, MD

**History**
LM initially presented in infancy for recurrent bullae and later developed enamel pits, delayed loss of primary teeth, loss of toenails and several fingernails, nail dystrophy, and corneal abrasions. Initial skin biopsy at birth revealed features suggestive of junctional epidermolysis bullosa (JEB) and epidermolysis bullosa simplex (EBS) on H&E and electron microscopy, respectively. In adolescence, he developed brown macules and patches on the trunk suggestive of EB nevi and chronic erosions in the nares. Genetic testing, once available, confirmed a type of epidermolysis bullosa. He additionally developed a non-healing ulcer on the left elbow.

**Past Medical History:** Dysphagia, constipation, anal fissures, recurrent corneal erosions, perianal fissures, right choroidal nevus near the optic nerve

**Family History:** Mother with type 2 diabetes mellitus, father with malignant melanoma

**Allergies:** None

**Medications:** None

**Physical Examination**
On the most recent exam, there are blisters and erosions on the plantar feet, lower legs, arms, and hands. There are superficial erosions and pink perifollicular papules on the scalp. Brown macules and patches on the right forearm, left upper arm, neck, and right lower back. All ten toenails and six fingernails are absent; the four remaining fingernails are dystrophic. No microstomia.

**Laboratory Data**
- Genetic testing: 2 heterozygous mutations on the COL17A1 gene: c.2407 G>T (G803X) leading to a premature termination codon, and c.994delG (V332C)
- CBC, CMP, CRP, iron studies, zinc, carotene, retinol, vitamin B12, and folate within normal limits
- ESR: 19 mm/hr (<15 mm/hr)

**Histopathology**
In 2016, a punch biopsy was performed of a non-healing, scaly hyperkeratotic hemorrhagic crusted plaque found on the left elbow. Histopathology revealed epidermal acanthosis with parakeratosis, acantholysis, and dyskeratotic cells without evidence of carcinoma, consistent with an acantholytic acanthoma.

**Treatment**
- 18-gauge needles for lancing blisters, mupirocin, Mepilex Lite for open wounds
- Ketoconazole shampoo, fluocinonide 0.05% solution for scalp
CASE 21
A 23-YEAR-OLD MAN WITH RECURRENT BLISTERS AND NAIL DYSTROPHY

Figure: (A) Open erosion with overlying hemorrhagic crust on left distal arm/elbow. (B) Several brown macules coalescing into patches on the right lower back suggestive of EB nevi. (C) Scaly hemorrhagic crusted plaque; biopsy taken. (D) and (E) Punch biopsy from the left elbow displayed acanthotic, hyperkeratotic epidermis with intraepidermal clefting, diffuse suprabasilar acantholysis and scattered dyskeratotic keratinocytes. In the context of a solitary lesion findings favored an acantholytic acanthoma. No evidence of carcinoma is identified.
GENERALIZED ATROPHIC BENIGN EPIDERMOLYSIS BULLOSA

Discussion

- Epidermolysis bullosa (EB) is an inherited skin fragility disorder caused by mutations of structural dermal-epidermal junction proteins.
- EB can be subdivided into 4 major groups based on the level of cleavage and defective proteins: epidermolysis bullosa simplex (EBS), junctional epidermolysis bullosa (JEB), dystrophic epidermolysis bullosa (DEB), and Kindler epidermolysis bullosa/Kindler Simplex (KS).
- Genetic testing is recommended to confirm the specific subtype and subsequent complications. Genetic testing can also reveal the types of pathogenic mutations leading to disease, such as nonsense mutations, which are nucleotide base substitutions leading to premature termination codons (PTC) and protein truncation. The type of mutation is important for potential therapeutic interventions.
- Generalized atrophic benign epidermolysis bullosa (GABEB), now termed generalized intermediate JEB, is a rare autosomal recessive form of junctional EB. Mutations in COL17A cause absent or decreased expression of type XVII hemidesmosomal transmembrane collagen, leading to frequent blisters, chronic wounds, and skin fragility without severe scarring. This subtype of EB is shown to have an excellent prognosis with proper management.
- Extracutaneous manifestations of GABEB/ generalized intermediate JEB include nail dystrophy, dental caries, alopecia, corneal erosions, and gradual vision loss. Oral blisters, esophageal strictures, GERD, and rectal fissures are several gastrointestinal manifestations. Squamous cell carcinoma due to chronic, non-healing wounds has been reported in patients with GABEB.
- This patient harbors a mutation resulting in a PTC and is therefore able to be treated with the novel drug ataluren. Ataluren is a well-tolerated, orally bioavailable, small molecule drug that enables the synthesis of a full-length functional protein through ribosomal PTC readthrough. It has been used in disorders with nonsense mutations and has been approved for treating Duchenne muscular dystrophy in Europe. Ataluren is only able to target PTCs without frameshift mutations. We are hopeful that ataluren treatment will help reduce the severity of our patient’s EB, and we look forward to beginning therapy in a clinical trial soon.

Teaching Points

- GABEB/generalized intermediate JEB is a rare autosomal recessive form of EB that results from mutations in COL17A, leading to absent or decreased expression of type XVII hemidesmosomal transmembrane collagen.
- This patient harbors a PTC from a single base substitution, making him eligible a clinical trial with ataluren.
- Ataluren is a novel small molecule drug that causes premature termination codon readthrough resulting in a functional protein, reducing disease severity and complications.

References

CASE 22
AN 18-YEAR-OLD WOMAN WITH PRURITIC, PAINFUL BULLAE OF THE SKIN, EYES AND ORAL MUCOSA

Patient

TS is an 18-year-old Albanian woman.

Presenters

Shiv Malhotra, MSII
Emilee Herringshaw, MSIV
Elana Putterman, MD
Karen Wiss, MD

History

An 18-year-old woman with a history of junctional epidermolysis bullosa (EB) was referred to our clinic to establish care. Over the past 15 years, she had been experiencing painful, pruritic, bullae and non-healing wounds on the fingers, toes, knees, elbows, and hips, with occasional erosions on her eyelids and oral mucosa. She also reported frequent dental caries, excessive sweating of the palms and soles, and chronic constipation. The earliest abnormal skin finding that the patient could recall was a solitary bulla on her right fifth digit shortly after birth. She was subsequently asymptomatic until age three. At age three, she developed many bullae on the skin, corneal abrasions, rapid loss of all fingernails and toenails, and dental caries. To alleviate symptoms, she typically ruptured bullae with a needle and drained the fluid with a syringe. She followed up regularly with a dentist and ophthalmologist. Prior to presentation at our multidisciplinary EB clinic, she was evaluated at an outside hospital and underwent genetic testing.

Past Medical History: Junctional EB

Family History: Older brother has clinically suspected, mild, generalized junctional EB

Allergies: None

Medications:

- Wounds: mupirocin 2% ointment for open skin, then cover with Telfa bandage/cotton socks
- Eyes: white petrolatum-mineral oil 57.3-42.5% nightly, and carboxymethylcellulose 0.5% eye drops daily as needed
- Teeth: sodium-fluoride-pot nitrate paste 1.1-5% for brushing teeth nightly

Physical Examination

There are bullae and erosions on the elbows, extensor knees, shins, fingers, and toes. There are scattered yellow hyperkeratotic plaques on the plantar soles. There were bullae and erosions on the upper and lower conjunctiva. There is loss of fingernails and toenails. The hair is normal. There is no microstomia. The estimated BSA for wounds is <1%. The estimated BSA for all skin findings is 8%.

Laboratory Data

- Vitamin A: 30 mcg/dL (normal), retinol binding protein: 2.4 mg/dL (normal), carotene: 17 mcg/dL (normal)
- Vitamin D: 25-OH, total: 25 ng/mL (low)
- GGT: 10 U/L (normal)
- Cystatin C: 0.81 mg/L (normal)
- eGFR: 86 mL/min/1.73m² (normal)
- CMP/CBC: WNL
- Iron, total: 126 mcg/dL (normal), iron binding capacity: 316 mcg/dL (normal), saturation: 40% (normal), ferritin: 14 ng/mL (normal)
- UA: WNL
- Genetics:
  - Variant 2: LAMA3, exon 33, c.4524+1G>A (hg19:chr18:21526249)

Treatment

- Rupture bullae with sterile needles as needed
- Apply Mepilex dressings and gentamicin ointment daily to open skin
- Apply 2Toms Blister Shield powder on palms and soles to reduce hyperhidrosis
- Recommend supportive footwear to minimize blister development
- Continue dental paste and lubricating eye drops and ointment
CASE 22
AN 18-YEAR-OLD WOMAN WITH PRURITIC, PAINFUL BULLAE OF THE SKIN, EYES AND ORAL MUCOSA

Figure: (A) Scattered healing erosions on the bilateral dorsal feet, and loss of all toenails. (B) Hyperkeratotic, macerated plaques on the right plantar foot. (C) Loss of all fingernails and healing erosions on the dorsal fingers.
JUNCTIONAL EPIDERMOLYSIS BULLOSAL

Discussion

- Junctional epidermolysis bullosa (JEB) is a form of EB that is classically characterized by generalized blistering that heals without scarring and often involves the perioral skin.
- In the classification of EB, JEB includes all subtypes of EB in which blisters develop within the lamina lucida of the basement membrane. JEB can be further classified into generalized and localized when describing the distribution of skin and mucosal involvement. In generalized JEB, large areas of the body are often involved, such as the trunk, extremities, and mucosal membranes. Localized JEB is often limited to particular regions of the body, such as the hands, elbows, knees, feet, or other areas.
- JEB is inherited in an autosomal recessive pattern. The specific gene mutation and protein implicated determine the extent of involvement and prognosis. Eight JEB subtypes have been identified, caused by mutations in seven distinct genes: LAMA3, LAMB3, LAMC2, COL17A1, ITGA6, ITGB4, and ITGA3. JEB is routinely diagnosed by conclusive molecular genetic testing.
- One mutation is a frameshift in the LAMA3 gene starting at the codon arginine 1273 on exon 29 (Arg1273GlyfsTer25 variant) to a glycine residue, resulting in a premature stop codon at position 25 of the new reading frame. This mutation has been reported once in the literature.
- The other mutation revealed a change in splicing in the LAMA3 gene seen on exon 33 (c.4524+1G>A) which appears to cause a loss of function in LAMA3 and contribute to JEB. This is the first report of this mutation in the literature.
- A multidisciplinary approach is highly beneficial for the management of JEB and can include specialists such as dermatologists, ophthalmologists, dentists, geneticists, and other providers to care for the different manifestations of the condition.

Teaching Points

- JEB is a heterogeneous group of disorders associated with significant morbidity and mortality. The mutation responsible for each subtype of JEB drives the extent and severity of presentation.
- Diagnosis is assisted by genetic testing, which can identify the specific mutation responsible for JEB. Novel variants responsible for the EB continue to be discovered with improved techniques for genetic sequencing. Reporting of variants and associated features will continue to inform the care provided to patients who live with EB.
- Mutations impacting the laminin 332 glycoprotein can be attributed to mutations in the LAMA3, LAMB3, or the LAMC3 gene that subsequently result in JEB. Various mutations, such as base pair substitutions, frame shifts, and splicing variations, can all result in a dysfunctional LAMA3 protein.
- Our patient demonstrates two rare mutations in the LAMA3 gene, which highlights the importance of considering additional variants and the complexity of genotype/phenotype correlation in patients suspected to have JEB.

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