27th Annual
John M Knox, MD
Memorial Lecture

Virtual Case Summaries

Cases presented by:

UT McGovern Medical School

Moderator: Misha Koshelev, MD, PhD, FAAD

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Case #1 – Sporotrichoid Surprise

Presenters: Alison Messer, MD, Richard Jahan-Tigh, MD, MS

HPI: 48-year-old man with rapidly progressive left-hand ulceration.

PMH: Recently diagnosed with rheumatoid arthritis and long-standing history of type 2 diabetes mellitus.

Medications: Etanercept, methotrexate, and prednisone started weeks prior to presentation. Not improving with oral antibiotics.

Physical Exam: Bilateral hand edema, left hand with ulceration with purulent drainage and eschar with surrounding erythema. Several hyperpigmented, indurated plaques and subcutaneous nodules on the bilateral lower extremities.

Case #1 – Sporotrichoid Surprise

Diagnosis: Disseminated sporotrichosis

Histopathology: Skin biopsies taken from the left hand, right thigh, and right shin all showed granulomatous inflammation with extensive necrosis. GMS stains showed small, cigar-shaped bodies in all specimens. Tissue cultures from the left hand, right thigh, and right shin all grew *Sporothrix schenckii* after 5 weeks.

Discussion: Sporotrichosis occurs via cutaneous exposure to dimorphic fungi including *Sporothrix schenckii*, and presents with fixed cutaneous, lymphocutaneous, and rarely, disseminated manifestations. This disease is sometimes known as the "Rose Gardener's Disease," referring to the fixed cutaneous presentation, in which a chancre-like lesion appears at the site of inoculation, usually from a thorn, splinter, plant, or soil carrying the fungi. The lymphocutaneous presentation is most common, evidenced by ulcerations that can progress to verrucous plaques. The rare disseminated form of sporotrichosis is usually associated with immunosuppression. It is particularly seen in patients with HIV-AIDS, alcoholism, hematological malignancies, and diabetes mellitus.

Infection must always be ruled out in patients receiving systemic immune suppression, especially as TNF-α inhibitors have emerged as leading therapies for many dermatologic (and rheumatologic) conditions. We performed three biopsies with tissue culture to increase the yield for diagnosis. Fortunately, given the patient's significant immunosuppression and extent of infection, all specimens revealed multiple organisms. We believe that this patient's diabetes may have predisposed him towards disseminated infection originally. In this case, we also see the importance of thorough history taking and physical examination. Only after the biopsy specimens suggested sporotrichosis did the patient remember to mention his fall onto thorns years before. He had reported a history of sporotrichosis but did not have any medical records to confirm this. Fortunately, with a full body skin examination, we were able to recognize his disseminated skin involvement and, in the setting of his immune suppression, strongly consider the possibility of atypical infections. Disseminated fungal infections are difficult to treat, often requiring years of antifungal therapy. There are no clinical trials for the treatment of disseminated sporotrichosis.

Treatment: The patient was started on amphotericin, then transitioned to itraconazole for outpatient maintenance therapy. However, due to unavailability of itraconazole at the time of discharge, voriconazole was instead prescribed. He continues to follow with infectious disease, who expect at least 12 months of therapy.

References:

1) Sizar & Talati, 2019. Sporotrichosis (Sporothrix schenckii). StatPearls
2) Conceição-Silva & Morgado, 2018. Immunopathogenesis of human sporotrichosis. Journal of Fungi
3) Verma, Verma, & Rattan, 2019. Lymphocutaneous sporotrichosis of face with verrucous lesions. Indian Dermatology Online J
4) Bonifaz & Tirado-Sánchez, 2017. Cutaneous disseminated and extracutaneous sporotrichosis. Journal of Fungi
5) Bonifazet al., 2018. Cutaneous disseminated sporotrichosis: JEADV

Case #2 – Ulcerated Nodule in a Woman with Cough and Shortness of Breath

Presenters: Kelly Wilmas, MD, Madeleine Duvic, MD

HPI: 71-year-old woman presents to ED with painful skin lesions on the left buttocks and left hip. The lesions have been present for 1 year, but recently enlarged and ulcerated. She reports associated symptoms of shortness of breath and cough. She was recently discharged from a hospital in Louisiana for pneumonia and a pulmonary embolism.

Medications: Bexarotene, topical clobetasol, bexarotene gel, levothyroxine, apixaban.

Physical Exam: Ulcerated nodule with eschar of the left buttock and oval erythematous, patches and plaques of bilateral buttocks.

Case #2 – Ulcerated Nodule in a Woman with Cough and Shortness of Breath

Diagnosis: Mycosis fungoides with large cell transformation and extracutaneous involvement

Histopathology: H&E showed large and atypical lymphoid dermal infiltrate with extensive epidermotropism. CD3+, CD4-, CD8-, TCR-β F1+ large atypical lymphocytes with CD4+ dendritic cells.

Discussion: Mycosis fungoides (MF) is the most common type of cutaneous T-cell lymphoma (CTCL). Prognosis in MF is typically determined by stage, i.e., the extent of body surface area involvement, type of cutaneous lesions, and presence of extra-cutaneous involvement. Large cell transformation (LCT) of MF is defined as the morphologic change from small/medium-sized atypical lymphocytes to a large variant, at least 4 times the normal size, encompassing greater than 25% of the total cell population in the skin or lymph nodes. The 5-year survival rate of patients with LCT is 38%, which is much lower than the 88% five-year survival rate of MF patients without LCT. One study found that the overall survival in patients with LCT was 11.88 years for those with a solitary tumor, 5.57 years in patients with multiple localized tumors, and 3.31 years in patients with multiple generalized tumors. Tumors were found in 85% of patients with LCT. A 31-year retrospective analysis demonstrated the development of LCT in 1.4% of stage I, 25% of stage IIB, and 50% of stage IV MF patients.

Mycosis fungoides can rarely progress to involve extracutaneous sites. Lung involvement in MF was seen in <1% of patients in one retrospective analysis of 710 CTCL patients. Approximately 50 cases of central nervous system (CNS) involvement in MF have been documented in the literature. It is important for physicians to be aware of the possibility of transformation and extra-cutaneous involvement, even in longstanding stage IA disease.

Treatment: While early stage mycosis fungoides patients are typically treated with skin directed therapy, patients with advanced stages typically require systemic therapy. This includes the use of retinoids like bexarotene, interferon, histone deacetylase inhibitors such as romidepsin, anti-CD30 antibodies such as brentuximab vedotin, and other chemotherapy or radiation.

Our patient received radiation to the lung mass and ulcerated tumor, with improvement of the lung mass on PET-CT, but with new skin tumors. She was treated with 50 mg etoposide with overall improvement. Eight months later, the patient presented to the ED with new neurologic symptoms and MF involvement of the CNS on MRI and LP. Patient then received palliative radiation and passed away.

References:

1) Pulitzer M, Myskowski PL, Horwitz SM, Querfeld C, Connolly B, Li J, Murali R. Mycosis fungoides with large cell transformation: clinicopathological features and prognostic factors. Pathology. 2014;46(7):610-6.
2) Jawed SI et al. Primary cutaneous T-cell lymphoma (mycosis fungoides and Sezary syndrome): part I. Diagnosis: clinical and histopathologic features and new molecular and biologic markers. J Am Acad Derm. 2014;70(2):205
3) Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, McCormack C. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood. 2008;112(8):3082-7.
4) Talpur R, Sui D, Gangar P, Dabaja BS, Duvic M. Retrospective Analysis of Prognostic Factors in 187 Cases of Transformed Mycosis Fungoides. Clin Lymphoma Myeloma Leuk. 2016;16(1):49-56.
5) Arulogun SO, Prince HM, Ng J, Lade S, Ryan GF, Blewitt O, McCormack C. Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. Blood. 2008;112(8):3082-7.
6) Baser S, Onn A, Lin E, Morice RC, Duvic M. Pulmonary manifestations in patients with cutaneous T-cell lymphomas. Cancer. 2007;109(8):1550-5.
7) Stein M, Farrar N, Jones GW, Wilson LD, Fox L, Wong RK, Kuten A. Central neurologic involvement in mycosis fungoides: ten cases, actuarial risk assessment, and predictive factors. Cancer J. 2006 Jan-Feb;12(1):55-62.
8) Fountain E, Mistry H, Jain P, Duvic M, Fowler N. Response to pembrolizumab and lenalidomide in advanced refractory mycosis fungoides. Leuk Lymphoma. 2019 Apr;60(4):1079-1082.

Case #3 – The Case of the Big Foot

Presenters: Daniel Grabell, MD, Richard Jahan-Tigh, MD, Stephen Tyring, MD, PhD, MBA

HPI: 44-year-old Hispanic man with a three-year history of uncontrolled type 2 diabetes presents for 3 months of left foot swelling. The patient reports that in the last week he has had increased pain.

PMH: Type 2 diabetes mellitus

Physical Exam: Left foot grossly enlarged when compared to right foot with fibrosis. On the plantar aspect of the left foot numerous verrucous papules are noted, some with hemorrhagic crusts.

Case #3 – The Case of the Big Foot

Diagnosis: *Mycobacterium tuberculosis* infection of the foot

Histopathology: Dermal fibrosis with hemosiderin. There are stasis changes in this biopsy. The biopsy findings are essentially non-contributory and the patient will likely need multiple repeat biopsies or a deep incisional biopsy.

AFB Culture: *Mycobacterium tuberculosis* complex

Discussion: Chronic, granulomatous infection of the subcutaneous and sometimes deeper tissues of the foot is commonly known as a mycetoma or Madura foot. It is classically caused by fungi including *Madurella mycetomatis*, *Pseudallescheria boydii,* and *Acremonium* species and termed eumycetoma. A similar presentation can also be caused by bacteria (termed actinomycetoma) including species of *Nocardia, Actinomadura, and Streptomyces.* Rarely, a mycetoma-like presentation is caused by acid-fast bacteria such as *Mycobacterium tuberculosis*.

The diagnosis of tuberculosis (TB) is classically made by a purified protein derivative (PPD) skin test, T-SPOT, or the QuantiFERON-TB Gold test. Recently the QuantiFERON-TB Gold Plus test was introduced which shows a higher sensitivity while maintaining the same specificity as the original test. Diagnosis of tuberculosis in infected skin as well as respiratory secretions can be achieved via culture, PCR-based assays, and staining for acid-fast bacteria.

Cutaneous manifestations of tuberculosis are divided into those caused by direct inoculation versus those caused by the spread of endogenous infection. Inoculation manifestations include the tuberculous chancre that represents lack of host immunity against TB and tuberculosis verruca cutis, which represents reinfection in a person with moderate to high TB-specific immunity. Manifestations caused by spread of endogenous infection include lupus vulgaris, scrofuloderma, orofacial tuberculosis, acute military tuberculosis, and tuberculous gummas. First line treatment includes rifampin, isoniazid, pyrazinamide, and ethambutol combined in multi-medication regimens.

Treatment: The patient was referred to infectious disease who will be initiating treatment.

References:

1) Bolognia J, Schaffer JV, Lorenzo, C. Dermatology. 4th ed. Mosby Elsevier, 2018.
2) James WD, Elston DM, Treat JR, Rosenbach MA, Neuhaus, IM. Andrews' Disease of the Skin Clinical Dermatology. 13th edition. Saunders Elsevier, 2020. Ch
3) Nayak B, Dash RR, Mohapatra KC, Panda G. Ankle and foot tuberculosis: a diagnostic dilemma. *J Family Med Prim Care*. 2014;3(2):129–131.

Case #4 - Another Sporotrichoid Spread

Presenters: Benjamin Freemyer, MD, Omar Pacha, MD

HPI: 62-year-old man presented with a painful rash on his left arm that started 4 weeks prior to presentation. It gradually spread up his left arm and to his right leg and left groin. A few days prior to the appearance of the rash, he was hunting and pierced his left arm with the bone of a wild hog.

PMH: Renal cell carcinoma, recently excised brain metastasis
Papillary thyroid carcinoma, treated with subtotal thyroidectomy
Small lymphocytic lymphoma, on active surveillance

Medications: Linezolid
Dexamethasone taper (for cerebral edema from recent neurosurgical intervention)

Physical Exam: Male in no acute distress. No cervical, axillary, or inguinal lymphadenopathy. Erythematous papules coalescing into plaques with induration and overlying scale on left arm, right leg, left groin. Lesions on the left arm appear to be spreading along the course of lymphatic channels

Case #4 - Another Sporotrichoid Spread

Diagnosis: Majocchi granuloma (MG)

Histopathology: Microscopic examination of a skin biopsy obtained from the left forearm revealed pseudoepitheliomatous hyperplasia with neutrophilic microabscesses and dermal fibrosis with lymphohistiocytic inflammation and giant cell reaction. Special stains (GMS, PAS, Gram, and Fite) detected no fungi or bacteria. A KOH prep of scales from the left forearm revealed many long, branch-like hyphae.

Discussion: Indurated papules and plaques with a KOH prep revealing fungal hyphae were highly suggestive of tinea corporis. Concurrent high dose systemic corticosteroids and skin trauma from hunting likely allowed invasion causing the indurated papules and plaques characteristic of MG. We opted to not biopsy initially so the histopathology results were after 2 weeks of terbinafine, which is likely why no fungal hyphae were seen on histology. The plaques on the left arm were progressing in a "sporotrichoid" pattern so sporotrichosis, *Mycobacteria marinum, Nocardia,* and cutaneous leishmaniasis were also considered. These were thought to be much less likely once tinea corporis was diagnosed.

MG is a dermal dermatophyte infection. This is often preceded by a superficial dermatophytosis that then invades in the setting of skin trauma or immunosuppression. In immunocompetent patients, perifollicular papules on the lower extremities are most often observed. In immunosuppressed patients the upper extremities are more commonly involved and granulomatous nodules are often seen. Diagnosis is confirmed on histopathology by finding fungal forms in the dermis or when a dermatophyte is grown on culture.

Treatment: Treatment consists of 1-6 months of oral antifungal therapy. Terbinafine is generally first line, but itraconazole, voriconazole, and griseofulvin have also been used. Our patient was treated with 6 weeks of oral terbinafine. He has only completed 5 weeks of therapy, but he has had resolution of the skin tenderness and a significant decrease in the size of his skin lesions.

References:

1) Bolognia JL, Schaffer, JV, Cerroni L. Dermatology. 4th ed. Philadelphia: Elsevier, 2018.

2) Rapini RP. Practical dermatopathology. Philadelphia: Elsevier Mosby, 2005.

3) Boral H, Durdu M, Ilkit M. Majocchi's granuloma: current perspectives. Infection and Drug Resistance. 2018; Volume 11:751-760.

Case #5 – Toupées: Friends or Foes?

Presenters: Vida Chitsazzadeh, MD, PhD, Omar Pacha, MD

HPI: 66-year-old man with AML admitted for stem cell transplantation seen as consultation regarding a lesion on left parietal scalp that was first noted after he removed his hairpiece. It has been enlarging for the past 2 days with associated burning sensation. He notes the lesion is the result of him scratching off the adhesives holding his toupee in place. He has low platelets and he gets a bruise every time his skin is traumatized.

PMH: Diabetes mellitus, diet controlled

FH: Not contributory

Medications:

Antimicrobials:
Liposomal amphotericin B 5mg/kg IV Q24H
Caspofungin 50mg IV Q24H
Cefepime 2g IV Q8H
Daptomycin 6mg/kg IV Q24H
Levofloxacin 500mg PO Q24H
Valacyclovir 500mg PO Q24H

Chemotherapy:
Cyclophosphamide 3,800 mg IVPB
Fludarabine 56.25 mg IVPB
Melphalan 93 mg IVPB

Immunosuppressants:
Mycophenolate mofetil 1g PO Q8H

Physical Exam: Left parietal scalp with a 4.2 x 2.5 cm hemorrhagic plaque with irregular surface, mottled areas of hemorrhage and necrosis. The wound was odorless and the surrounding area was warm, erythematous, and indurated.

Case #5 – Toupées: Friends or Foes?

Diagnosis: Cutaneous mucormycosis

Histopathology: Microscopic examination of biopsies obtained from the lesion on the left parietal scalp showed skin and subcutaneous tissue with acute and chronic inflammatory infiltrate and numerous fungal organisms (hyphae and spores) with angioinvasion. GMS stain highlighted fungal organisms with irregular, broad to variable sized hyphae. Immunohistochemical stains with anti-*Rhizopus* and anti-*Aspergillus* antibodies were performed. The fungal organisms were positive for anti-*Rhizopus* antibodies, supporting fungal organisms of *Mucor* family.

Discussion: Erythema and induration at the site of inoculation are usually the presenting signs of cutaneous mucormycosis. The angioinvasive organisms result in tissue infarction that manifests as a black eschar with central ulceration. A severe complication of this disease is necrotizing fasciitis. The causative organisms belong to the order *Mucorales*, which are ubiquitous, saphrophytic, and thermotolerant fungi. They can form spores and can grow rapidly in 2-5 days. *Mucorales* are further classified into six families. The most common family implicated in human disease is *Rhizopus*.

Infection can occur via inhalation, ingestion, or direct inoculation of spores. Diagnosis is confirmed by biopsy and culture. Characteristically, histopathology reveals non-septate, wide-angled branching, broad hyphae. Fungal blood cultures are usually negative, and serological testing is not reliable.

Cutaneous mucormycosis generally affects hosts with significantly compromised skin integrity (burn victims) or those with impaired immune systems. The latter include patients with diabetes, transplant recipients, and those with chronic steroid use. Skin infection may lead to hematogenous spread.

Treatment: Treatment of cutaneous mucormycosis includes aggressive surgical debridement and antifungal therapy. Surgical debridement is necessary to minimize deeper extension and dissemination of infection; sometimes, this can only be achieved through serial surgical debridement. The only FDA-approved antifungal therapies for cutaneous mucormycosis are either amphotericin B deoxycholate at high doses (1.0-1.5mg/kg/day); or lipid formulations of amphotericin B, with the latter being the preferred therapy. In addition, posaconazole have been shown to be successful as salvage therapy, when administered either as 200 mg four times daily or

400 mg twice daily. Hyperbaric oxygen treatment may also be used as an adjunctive therapy; however, there are no randomized clinical trials to support wide use of this modality.

In our patient's case, the infectious disease team was consulted and he was started on liposomal amphotericin B and posaconazole. MRI of the brain was obtained and showed enhancement in the left parietal scalp extending from the skin surface to the subgaleal space compatible with known mucormycosis with no evidence of underlying bony involvement or intracranial extension. Plastic surgery was consulted and excision of the lesion was completed with a split thickness skin graft from left thigh donor site.

References:

1) Kontoyiannis, D.P. and R.E. Lewis, Invasive zygomycosis: update on pathogenesis, clinical manifestations, and management. Infect Dis Clin North Am, 2006. 20(3): p. 581-607.
2) Chayakulkeeree, M., M.A. Ghannoum, and J.R. Perfect, Zygomycosis: the re-emerging fungal infection. Eur J Clin Microbiol Infect Dis, 2006. 25(4): p. 215-29.
3) Spellberg, B., J. Edwards, Jr., and A. Ibrahim, Novel perspectives on mucormycosis: pathophysiology, presentation, and management. Clin Microbiol Rev, 2005. 18(3): p. 556-69.
4) Roden, M.M., et al., Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis, 2005. 41(5): p. 634-53.

Case #6 – Consult for a Changing Chest

Presenters: Jordan Buckley, MD, Sharon Hymes, MD

HPI: 38-year-old female with history of right-sided breast cancer presents with "breast asymmetry." Over the past 6 months the right breast has changed shape and appears contracted and smaller than the left breast. In addition, the skin of lateral aspect of the right breast has become shiny, dark, and firm.

PMH: Invasive ductal carcinoma of the right breast s/p chemotherapy with pertuzumab, carboplatin, trastuzumab in 2017 and radiation to right breast and axillary nodal basin; 50Gy in 25 fractions, followed by 10Gy in 5 fractions in 2018. Treated with maintenance pertuzumab and trastuzumab through 6/2018.
Hypothyroidism

PSH: Breast augmentation with bilateral silicone implants in 2012.
Right partial mastectomy and excision of 3 axillary nodes in 10/2017 with subsequent breast augmentation and bilateral implant replacement.

FH: No family history of breast cancer, autoimmune, or rheumatologic disease.

Physical Exam: Lateral half of right breast with hyperpigmented, indurated, hairless, shiny patch.
Well healed surgical scars inferior to bilateral breasts.
Remainder of exam within normal limits.

Case #6 – Consult for a Changing Chest

Diagnosis: Radiation induced morphea

Histopathology: Microscopic examination of biopsy obtained from the plaque on the right lateral breast demonstrated intact epidermis, papillary dermis with a focal perivascular lymphoplasmacytic infiltrate, and reticular dermis with thickened eosinophilic collagen bundles.

Discussion: Radiation induced morphea is a rare complication of radiation therapy. This disorder is characterized by skin changes including sclerosis, erythema, and pigmentary alterations within a radiation field, and sometimes beyond it. The incidence is about 1 in 500 patients treated with radiation, and it is reported most commonly in those treated for breast cancer. Disease onset is most common within one year of irradiation, but can occur several years afterwards.

The pathogenesis of this disease is poorly understood. It has been proposed that disturbance of cytokine pattern may play a role. After radiation exposure, Th2 cytokines are secreted, which include IL-4 and IL-5. These stimulate collagen synthesis as well as the production of TGF-β. TGF-β has a role in tissue repair, but pathologic secretion of TGF-β may lead to extensive fibrosis.

Risk factors for the development of radiation induced morphea are largely unknown, but may include autoimmune disease, most commonly rheumatoid arthritis. Studies have shown that more severe disease is associated with obesity, smoking history, breast implantation, and autoimmune disorders. There also may be a relationship with surgery, as the majority of patients who develop radiation induced morphea had a surgical procedure prior to radiation. Interestingly, the type and dose of radiation has not been found correlate with the extent of disease.

Diagnosis is made by skin biopsy. In addition to the changes of radiation dermatitis, pathology demonstrates perivascular and subcutaneous inflammation with dermal fibrosis and collagen deposition.

Treatment options consist of topicals, phototherapy, and systemic drugs. Topical steroids, calcineurin inhibitors, and vitamin D analogues are often used for mild disease. Phototherapy including UVA and nbUVB is also frequently used in combination with topical medication. Systemic options include steroids, methotrexate, mycophenolate, celecoxib, and tofacitinib. Patients respond best to a combination of treatment modalities although this disease often has unsatisfactory treatment results. Patients with active

inflammatory disease at the time of treatment initiation are more likely to respond than those with burned out disease.

Treatment: We prescribed clobetasol 0.05% cream to apply to the affected area of the right breast twice daily. The patient has been using this regimen for 4 weeks and reports mild improvement with decreased firmness of the affected area. If there is insufficient response to topical steroids, we discussed future possibilities of UVA light therapy, oral steroids, or methotrexate. We also recommended that she avoid further surgical procedures of the right breast as this may contribute to the disease process.

References:

1) Bolognia JL, Schaffer, JV, Cerroni L. Dermatology. 4th ed. Philadelphia: Elsevier, 2018.

2) Lever WF, Elder DE. Lever's histopathology of the skin. 10th ed. Philadephia: Wolters Kluwer/Lippincott Williams & Wilkins, 2009.

3) Rapini RP. Practical dermatopathology. Philadelphia: Elsevier Mosby, 2005.

4) Mittal, A, et al. Radiation-induced morphea: Association with autoimmune comorbidities, severity, and response to therapy. Journal of the American Academy of Dermatology, Volume 81, Issue 1, 260 – 262.

5) Dyer, BA, Hodges, MG, and Mayadev, JS. "Radiation-Induced Morphea: An Under-Recognized Complication of Breast Irradiation." Clinical Breast Cancer 16.4 (2016): e141–e143. Web.

6) Spalek, M, Jonska-Gmyrek, J, and Gałecki, J. "Radiation-Induced Morphea - a Literature Review." Journal of the European Academy of Dermatology and Venereology: JEADV 29.2 (2015): 197–202. Web.

7) Herrmann T, Gunther C, Csere P. Localized morphea–a rare but significant secondary complication following breast cancer radiotherapy. Case report and review of the literature on radiation reaction among patients with scleroderma/morphea. Strahlenther Onkol 2009; 185: 603–607.

8) Friedman, Or, Barnea, Yoav, and Hafner, Ariela. "Underdiagnosed and Disfiguring - Radiation-Induced Morphea Following Breast Cancer Treatment." The Breast 39 (2018): 97–100. Web.

Case #7 – 19-year-old Woman with a Prickly Nose

Presenters: Ritu Swali, MD, Stephen Tyring, MD, PhD, MBA

HPI: 19-year-old Caucasian female presents with a five-month history of spiny projections located on the tip of her nose.

PMH: Depression, anxiety, and recent acute systolic heart failure with subsequent transplant

FH: Non-contributory

Medications: Prednisone, tacrolimus, mycophenolate mofetil

Physical Exam: Folliculocentric papules with white, protruding spiculations on the nasal apex and dorsum. Erythematous papules and nodules with scattered pustules on the face.

Case #7 – 19-year-old Woman with a Prickly Nose

Diagnosis: Trichodysplasia spinulosa (TS)

Histopathology: Obtained prior to presentation at another facility

Discussion: Trichodysplasia spinulosa (TS) is a rare dermatologic condition with fewer than 40 reported cases. It is characterized by folliculocentric papules and keratin projections in immunocompromised individuals. In the last decade, trichodysplasia spinulosa-associated polyomavirus (TSPyV), a small double-stranded DNA virus, has been identified as clonally integrated in TS-affected cells, with anti-TSPyV immunostaining localizing expression to TS-affected follicular keratinocytes. A proposed mechanism of action involves dysregulation of MEK, ERK, and MNK1 by interacting with protein phosphatase 2A. Diagnosis of TS is largely clinical, with a confirmatory biopsy. Histopathologic examination classically reveals dilated and distorted hair follicles, disorganized inner root sheath cell hyperproliferation with abnormally large trichohyalin granules, and gray-blue cytoplasmic material occupying most of the follicular epithelium.

TSPyV transmission and pathogenesis are not well understood; however, viral detection in nasopharyngeal and fecal sampling implies respiratory and/or fecal-oral routes. Additionally, while polyomaviruses are thought to manifest upon viral reactivation during immunosuppression, anti-TSPyV IgG is only detected following clinical evidence of TS, suggesting that the disease state in TS is caused by primary infection rather than reactivation. Interestingly, although TS is a disease of the immunocompromised, it has not been reported in the elderly, an observation that further supports primary infection rather than reactivation.

We describe a 19-year-old female heart transplant patient on mycophenolate mofetil, tacrolimus, and prednisone who developed TS. There are only four other cases known to the authors of TS developing in cardiac transplant recipients: a 15-year-old male on mycophenolate mofetil, tacrolimus, and prednisone; a 5-year-old male on mycophenolate mofetil, tacrolimus, and prednisone; a 5-year-old female on mycophenolate mofetil and tacrolimus; and a 6-year-old male on mycophenolate mofetil, tacrolimus, and prednisone. It is interesting to note that all of the reported patients, including ours, were on aggressive immunosuppressive regimens including mycophenolate mofetil and tacrolimus. Detection of TSPyV in the cardiac tissue of a 7-month-old female with fatal myocarditis also raises the question whether this polyomavirus plays a role in the pathology necessitating organ transplant.

Treatment: An efficacious, curative TS therapy has yet to be reported. As permitted, TS treatment involves manual extraction of keratin projections, topical cidofovir, oral valganciclovir, oral leflunomide, and reduction of immunosuppressive agents; spontaneous resolution has also been reported. Topical keratolytics, oral minocycline, and topical and oral retinoids have been trialed with limited success. One similar case report describes minimal improvement with imiquimod, though combination therapy with topical retinoids has not been reported. Since our patient previously failed oral valganciclovir, a trial of combination tazarotene 0.1% cream and imiquimod 5% cream was crafted due to prohibitive costs and compounding requirements of topical cidofovir in addition to extensive scar risk with manual extraction. Imiquimod stimulates the host's innate and acquired immune responses (e.g., antiviral responses). Although the utility of imiquimod is traditionally thought to be limited in immunosuppressed patients, we considered that the patient had likely been infected with the virus prior to disease manifestation and that imiquimod has demonstrated efficacy in verrucous diseases in HIV-positive individuals. Ultimately, it is plausible that immunosuppression resulted in the slowed, partial clinical improvement seen in this patient. The patient was subsequently switched to topical cidofovir 3%, with plans for close follow up.

References:

1) DeCrescenzo AJ, Philips RC, Wilkerson MG. Trichodysplasia spinulosa: a rare complication of immunosuppression. JAAD Case Rep 2016;2(4):307-9.
2) Wanat KA, Holler PD, Dentchev T, et al. Viral-associated trichodysplasia: characterization of a novel polyomavirus infection with therapeutic insights. Arch Dermatol 2012;148(2):219-23.
3) Sheu JC, Tran J, Rady PL, Dao H Jr, Tyring SK, Nguyen HP. Polyomaviruses of the skin: integrating molecular and clinical advances in an emerging class of viruses. Br J Dermatol 2019;180(6):1302-11.
4) van der Meijden E, Janssens RW, Lauber C, Bouwes Bavinck JN, Gorbalenya AE, Feltkamp MC. Discovery of a new human polyomavirus associated with trichodysplasia spinulosa in an immunocompromized patient. PLoS Pathog 2010;6(7):e1001024.
5) Rouanet J, Aubin F, Gaboriaud P, et al. Trichodysplasia spinulosa: a polyomavirus infection specifically targeting follicular keratinocytes in immunocompromised patients. Br J Dermatol 2016;174(3):629-32.
6) Wu JH, Narayanan D, Simonette RA, Rady PL, Tyring SK. Dysregulation of the MEK/ERK/MNK1 signalling cascade by middle T antigen of the trichoydsplasia spinulosa polyomavirus. J Eur Acad Dermatol Venereol 2017;31(8):1338-41.
7) Matthews MR, Wang RC, Reddick RL, Saldivar VA, Browning JC. Viral-associated trichodysplasia spinulosa: a case with electron microscopic and molecular detection of the trichodysplasia spinulosa-associated human polyomavirus. J Cutan Pathol 2011;38(5):420-31.
8) Siebrasse EA, Bauer I, Holtz LR, et al. Human polyomaviruses in children undergoing transplantation, United States, 2008-2010. Emerg Infect Dis 2012;18(10):1676-9.
9) van der Meijden E, Kazem S, Burgers MM, et al. Seroprevalence of trichodysplasia spinulosa-associated polyomavirus. Emerg Infect Dis 2011;17(8):1355-63.
10) Benoit T, Bacelieri R, Morrell DS, Metcalf J. Viral-associated trichodysplasia of immunosuppression: report of a pediatric patient with response to oral valganciclovir. Arch Dermatol 2010;146(8):871-4.
11) Schwieger-Briel A, Balma-Mena A, Ngan B, Dipchand A, Pope E. Trichodysplasia spinulosa--a rare complication in immunosuppressed patients. Pediatr Dermatol 2010;27(5):509-13.
12) Stephan C, Kurban M, Khalil S, Bitar F, El-Rassi I, Assy J. Viral-associated trichodysplasia spinulosa in a paediatric cardiac transplant recipient. Clin Exp Dermatol 2019. doi: 10.1111/ced.14017.
13) Tsuzuki S, Fukumoto H, Mine S, et al. Detection of trichodysplasia spinulosa-associated polyomavirus in a fatal case of myocarditis in a seven-month-old girl. Int J Clin Exp Pathol 2014;7(8):5308-12.
14) Wu JH, Nguyen HP, Rady PL, Tyring SK. Molecular insight into the viral biology and clinical features of trichodysplasia spinulosa. Br J Dermatol 2016;174(3):490-8.

15) van der Meijden E, Horváth B, Nijland M, et al. Primary polyomavirus infection, not reactivation, as the cause of trichodysplasia spinulosa in immunocompromised patients. J Infect Dis 2017;215(7):1080-4.
16) Leitenberger JJ, Abdelmalek M, Wang RC, Strasfeld L, Hopkins RS. Two cases of trichodysplasia spinulosa responsive to compounded topical cidofovir 3% cream. JAAD Case Rep 2015;1(6):S33-5.
17) Aleissa M, Konstantinou MP, Samimi M, et al. Trichodysplasia spinulosa associated with HIV infection: clinical response to acitretin and valganciclovir. Clin Exp Dermatol 2018;43(2):231-3.
18) Izakovic J, Büchner SA, Düggelin M, Guggenheim R, Itin PH. Hair-like hyperkeratoses in patients with kidney transplants. A new cyclosporin side-effect. Hautarzt 1995;46(12):841-6.
19) Sadler GM, Halbert AR, Smith N, Rogers M. Trichodysplasia spinulosa associated with chemotherapy for acute lymphocytic leukaemia. Australas J Dermatol 2007;48(2):110-4.
20) Campbell RM, Ney A, Gohh R, Robinson-Bostom L. Spiny hyperkeratotic projections on the face and extremities of a kidney transplant recipient. Arch Dermatol 2006;142(12):1643-8.
21) Lee JS, Frederiksen P, Kossard S. Progressive trichodysplasia spinulosa in a patient with chronic lymphocytic leukaemia in remission. Australas J Dermatol 2008;49(1):57-60.
22) Sperling LC, Tomaszewski MM, Thomas DA. Viral-associated trichodysplasia in patients who are immunocompromised. J Am Acad Dermatol 2004;50(2):318-22.
23) Vidal D. Topical imiquimod: mechanism of action and clinical applications. Mini Rev Med Chem 2006;6(5):499-503

Case #8 – Bad Bulla

Presenters: Katherine Martin MD, Tony Nguyen, MD

HPI: A 26-year-old previously healthy man presented to the emergency center for a new rapidly enlarging lesion on the left lower extremity. This had started 4 days prior to presentation as a lesion that the patient described as resembling a pimple. He also noted a two-week history of fatigue, headache, and decreased appetite.

PMH: None

Medications: Occasional NSAIDs for headaches

Physical Exam: On initial evaluation, the patient had a large violaceous indurated bullous plaque with well-demarcated borders and surrounding erythema overlying most of the right shin. The skin was otherwise clear with no additional lesions.

Case #8 – Bad Bulla

Diagnosis: Bullous Pyoderma Gangrenosum

Histopathology: Microscopic examination of a punch biopsy obtained from the periphery of the lesion on his left lower leg revealed a dermal neutrophilic infiltrate with extravasated erythrocytes. Bacterial, acid-fast bacilli, and fungal cultures were negative.

Discussion: Pyoderma gangrenosum is a sterile neutrophilic dermatosis of unknown etiology that is seen with numerous systemic diseases including inflammatory bowel disease, rheumatoid arthritis, and hematological malignancies. Pyoderma gangrenosum has been classically subdivided into four types: ulcerative, pustular, bullous, and superficial granulomatous.

Bullous pyoderma gangrenosum typically presents on the extremities as bullae, which expand rapidly in a concentric pattern. Bullous pyoderma gangrenosum has a particularly close association with hematological malignancies and is often seen in aggressive cases of leukemia, emphasizing the importance of a timely diagnosis and thorough hematologic evaluation. Diagnosis is typically made based on clinical features and the rapid progression of the lesion. Histopathological evaluation of pyoderma gangrenosum may be nonspecific and is primarily characterized by a neutrophilic infiltrate often with leukocytoclasia; it may also include subepidermal hemorrhagic bullae in the case of the bullous variant. Infection must be ruled out. The clinical appearance and pathological evaluation can have considerable overlap with the superficial bullous variant of Sweet Syndrome, which can also be seen in patients with hematological malignancies.

Treatment: Treatment of the underlying hematologic disorder typically helps these lesions. Systemic corticosteroids, cyclosporine, methotrexate, azathioprine dapsone, and cyclophosphamide have also been used with success.

Our patient improved with initiation of systemic steroids and fludarabine and venetoclax chemotherapy.

References:

1) Neil Crowson, A., Martin C. Mihm Jr, and Cynthia Magro. "Pyoderma gangrenosum: a review." Journal of Cutaneous Pathology 30.2 (2003): 97-107.

2) Powell, Frank C., WP Daniel Su, and Harold O. Perry. "Pyoderma gangrenosum: classification and management." Journal of the American Academy of Dermatology 34.3 (1996): 395-409.

3) Perry, Harold O., and Richard K. Winkelmann. "Bullous pyoderma gangrenosum and leukemia." Archives of Dermatology 106.6 (1972): 901-905.

4) Chung, Vinh Q., et al. "Clinical and pathologic findings of paraneoplastic dermatoses." Journal of the American Academy of Dermatology 54.5 (2006): 745-762.

Case #9 – Precarious Papules

Presenters: Nader Aboul-Fettouh MD, Sharon Hymes MD

HPI: 66-year-old man referred for consultation regarding new tender, occasionally pruritic lesions on the groin and lower extremities.

PMH: Langerhans cell sarcoma of left lateral hip s/p local radiation and chemotherapy in complete remission.

Physical Exam: Pink, eroded, dome shaped papules on the scrotum, left medial inner thigh, right flank, and right posterior thigh.

Case #9 – Precarious Papules

Diagnosis: Langerhans cell histiocytosis / Langerhans cell sarcoma

Pathology: H&E showed proliferation of tumor cells with cytologic atypia involving the dermis and extending into the epidermis. The cells revealed bean-shaped nuclei and ample cytoplasm, consistent with histiocytic/Langerhans cells lineage. High mitotic rate and atypical mitotic figures were seen. Immunohistochemistry showed cells that were diffusely positive for CD1a, langerin, and S100. Staining was negative for Sox-10.

Therapy: Previous disease treated with radiation with recurrence followed by cytarabine, etoposide, lenalidomide, followed by gemcitabine and docetaxel.

Discussion: LCH is a rare disorder due to aberrant proliferation of Langerhans cells in a variety of organ systems including bone, skin, lungs and the central nervous system. The incidence is 4.6 cases in million in children and 1 to 2 cases per million in adults. Skin manifestations include solitary lesions, multiple brown or purplish papules in infants, or widespread eczematous rashes or ulcerative lesions in intertriginous areas. BRAF mutations have been found in 57% of LCH lesions. Lesions in histiocytic sarcoma are more aggressive than typical LCH lesions, with histologic features of macrophage-monocyte lineage, CD68 and CD163 positivity, and a higher mitotic index.

At time of diagnosis, patients are risk stratified based on extent of disease and organ system involvement. Single system LCH in the skin can be treated with methotrexate, 6-mercaptopurine, or hydroxyurea. Skin-limited lesions have responded to topical steroids and nitrogen mustard. Patients with multisystem LCH typically undergo intensive chemotherapy, including vinblastine plus prednisolone or cytarabine alone, with the goal of achieving complete resolution of signs and symptoms. Targeted therapies including BRAF inhibitors have had some success although many patients have had early relapse. Clinical trials are underway to identify treatments with better control of this disease.

References:

1) Allen CE, Merad M, McClain KL. Langerhans-Cell Histiocytosis. N Engl J Med. 2018;379(9):856–868. doi:10.1056/NEJMra1607548
2) Grana, N.. Langerhans Cell Histiocytosis. Cancer Control 2014, 328–334. https://doi.org/10.1177/107327481402100409
3) Kobayashi M, Tojo A. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. Cancer Sci. 2018;109(12):3707–3713. doi:10.1111/cas.13817

Case #10 – The Black Eye

Presenters: Harina Vin, MD, Susan Chon, MD

HPI: 67 yo female from Texas with history of relapsed diffuse large B-cell lymphoma (DLBCL) and chronic hepatitis B presents to the emergency department for fatigue and new skin lesions. One month prior to presentation, she was hospitalized for preseptal cellulitis of the left eye thought to have originated from a boil near the left eyebrow.

Medications:
Venetoclax 200mg daily
Ibrutinib 280mg daily
Tenofovir 300mg daily
Voriconazole 200mg BID
Valacyclovir 500mg daily
Atorvastatin 20mg daily
Losartan 100mg daily
Metformin 1000mg BID
Vitamin D3 2000 International Units daily
Insulin: aspart 5-15 units TID and glargine 18 units nightly
Promethazine 12.5mg q8 hours PRN

Physical Exam: Ulcerated plaques with erythematous borders and black eschars on the forehead and left medial inferior eyebrow

Case #10 – The Black Eye

Diagnosis: Ecthyma gangrenosum (EG)

Histopathology: H&E showed ulceration and dermal acute and chronic inflammation. Fite, Gram, and GMS stains were negative.

Discussion: Ecthyma gangrenosum is caused by *Pseudomonas aeruginosa*, a Gram-negative opportunistic pathogen that typically infects immunocompromised patients. Typical EG lesions appear as necrotic ulcers with erythematous borders, predominantly affecting the axillary and anogenital areas. The arms, legs, trunk, and face can also be involved.

The presence of ecthyma gangrenosum is indicative of a severe systemic infection; only a small number of cases have been reported in nonbacteremic patients. There is debate whether lesions diagnosed as ecthyma gangrenosum, but with bacteremia due to other bacterial or fungal species, are actually EG or if ecthyma gangrenosum is pathognomonic of *Pseudomonas* septicemia. Nevertheless, the most important prognostic factor of mortality in invasive forms is the presence of neutropenia at diagnosis.

There are a handful of cases in the literature of endogenous seeding of the *Pseudomonas* to orbit and eye. Most published cases required surgical debridement or intravitreal antibiotics in addition to intravenous antibiotics; however, our patient's orbital symptoms resolved with systemic antibiotics alone. Early recognition of endogenous ophthalmic disease is critical because prognosis of combined orbital cellulitis and panophthalmitis is poor and can require enucleation.

Treatment: Antibiotic therapy for *Pseudomonas aeruginosa* includes aminoglycosides, third- and fourth-generation cephalosporins, β-lactam antibiotics, and broad-spectrum penicillins. Tissue cultures provide the advantage of susceptibility testing. Some studies comparing combination therapy with monotherapy reveal that the regimens do not affect mortality rates.

Our patient's orbital cellulitis markedly improved with systemic antibiotics but she continued to get new ecthyma gangrenosum lesions. Despite re-admission for IV broad spectrum antibiotics, her mental status gradually declined and she eventually passed away 14 days into the second admission.

References:

1) Martínez-Longoria CA, Rosales-Solis GM, Ocampo-Garza J, Guerrero-González GA, Ocampo-Candiani J. Ecthyma gangrenosum: a report of eight cases. An Bras Dermatol. 2017;92(5):698–700.
2) Huminer D, Siegman-Igra Y, Morduchowicz G, Pitlik SD. Ecthyma gangrenosum without bacteremia. Report of six cases and review of the literature. Arch Intern Med. 1987; 147(2):299-301.
3) Luemsamran P, Pornpanich K, Vangveeravong S, Mekanandha P. Orbital cellulitis and endophthalmitis in pseudomonas septicemia. Orbit. 2008; 27(6):455-7
4) Hulten, EA, Shah, AA, Petersen, KN, Gallagher, CM, Vangeertruyden, PH, & Kortepeter, MG. Pseudomonas aeruginosa preseptal cellulitis and focal necrosis in a patient with severe immunocompromise. Infectious Diseases in Clinical Practice. 2009; 17(5), 346-348.
5) Vaiman M, Lazarovitch T, Heller L, Lotan G. Ecthyma gangrenosum and ecthyma-like lesions: review article. Eur J Clin Microbiol Infect Dis. 2015; 34(4):633-9.

Case # 11 – Wart Puzzle

Presenters: Fiona Muhaj, MD, Natasha Klimas, MD, Tony Nguyen, MD

HPI: A healthy 24-year-old Hispanic woman presented for evaluation of multiple symmetric lesions of the groin and vulva. These had been present for eight years with occasional pruritus and burning. The patient was under the impression these were genital warts and had not pursued any treatment until recently. She was up to date on her Pap smear, the most recent one showing low-grade cervical intraepithelial neoplasia.

FH: There is reported history of similar lesions in the mother and maternal uncle. The family members had not sought medical advice.

Physical Exam: Exam showed multiple skin-colored to violaceous flat-topped papules, some coalescing into plaques, extending from bilateral medial thighs to the labia majora. On the central chest there were a few faintly erythematous to hyperpigmented, thin, scaly plaques. No intertriginous involvement of inframammary or axillary folds was noted. Mucosae, palms, soles, and nails were normal.

Case #11 – Wart Puzzle

Diagnosis: Papular acantholytic dyskeratosis (PAD)

Histopathology: Microscopic examination from a lesion on the right medial thigh demonstrated hyperkeratosis, full thickness intraepidermal acantholysis, and multiple dyskeratotic cells within the granular layer. There was a sparse perivascular lymphocytic infiltrate.

Discussion: Papular acantholytic dyskeratosis (PAD) is a rare entity initially reported in 1985. It presents as an eruption of skin colored to whitish papules and plaques limited to the genitocrural or the anogenital region of both sexes. In females the lesions favor the vulva and there have been reports of chest involvement.

The diagnosis requires clinico-pathologic correlation: the often-suspected clinical differentials such as condylomata acuminata and less frequently lichen planus or lichen simplex chronicus do not fit with the acantholytic dyskeratosis seen on histopathology. This often leaves the clinician with the challenge of distinguishing PAD from Hailey-Hailey disease (HHD) and Darier disease.

Our patient's biopsy showed multiple dyskeratotic cells but there were no other clinical features suggestive of Darier disease. Although there was family history of a similar eruption, thus raising the possibility of HHD, the absence of erosions, macerated plaques, and lack of past history of superimposed fungal or bacterial infections made HHD a less favorable clinical diagnosis. Additionally, isolated vulvar HHD is rare and is most likely to be found in the setting of concomitant disease elsewhere. To further cloud the picture, there are reports of familial PAD.

It is now known that PAD results from mutations involving the ATP2C1 gene, which encodes the Golgi hSPCA1 pump that is defective in HHD. The two conditions are thought to be allelic, where the same isolated APT2C1 mutation can lead to different clinical phenotypes. Despite the shared genetic basis, the different clinical severity of the two diseases carries significant impact in patients' quality of life.

Treatment: The treatment for PAD is not standardized. Given the shared genetic basis with HHD, it is not unreasonable to extrapolate treatment modalities. There are reports of PAD (and HHD) lesion improvement with topical tacrolimus 0.1% ointment; however, adherence depends on patients' tolerance to treatment. More recently, low dose naltrexone and magnesium chloride have been favored for managing HHD due to anti-inflammatory properties and postulated regulatory effect in calcium homeostasis, respectively.

Our patient was started on topical tacrolimus 0.1% ointment and on a systemic regimen of naltrexone 25mg daily and magnesium chloride 250mg daily. Our future options include oral isotretinoin if there is no noted improvement at follow up. This systemic therapy has been found effective in a few cases of PAD with widespread or resistant lesions.

References:

1) Al-Muriesh, M. , Abdul-fattah, B. et al. Papular acantholytic dyskeratosis of the anogenital and genitocrural area: case series and review of the literature. J Cutan Pathol, 43: 749-758 (2016)
2) Roh, M. R., Choi, Y. J. and Lee, K. G. Papular acantholytic dyskeratosis of the vulva. The Journal of Dermatology, 36: 427-429. (2009)
3) Vodo, D. , Malchin, N. , Furman, M. , Sarig, O. and Sprecher, E. Identification of a recurrent mutation in ATP2C1 demonstrates that papular acantholytic dyskeratosis and Hailey–Hailey disease are allelic disorders. Br J Dermatol, 179: 1001-1002. (2018)
4) Wieselthier JS, Pincus SH. Hailey-Hailey Disease of the Vulva. Arch Dermatol,129(10):1344–1345. (1993)
5) Alajmi, Ali et al. “Hailey-Hailey disease treated successfully with naltrexone and magnesium.” JAAD case reports vol. 5,9 760-762. (2019)

Case #12 – Surprise in the Delivery Room

Presenters: Mary DarConte, MD, Adelaide Hebert, MD

HPI: Male newborn with right leg mass not detected on prenatal ultrasound

Birth Hx: Born at 34 2/7 weeks via C-section for severe intrauterine growth restriction

Physical Exam: 8.4 cm violaceous mass of right thigh

Case # 12 – Surprise in the Delivery Room

Diagnosis: Kaposiform hemangioendothelioma (KHE)

Discussion: Kaposiform hemangioendothelioma is a rare vascular anomaly most commonly diagnosed during early childhood. Over half of patients with KHE can develop or present concomitantly with Kasabach-Merritt Phenomenon (KMP). KMP can manifest as severe thrombocytopenia with a consumptive coagulopathy. This puts the patient at risk for hemorrhages and other sequelae if not identified early. Due to this, it is important to distinguish KHE from other more common vascular anomalies with a benign course.

Our patient presented at birth with a large subcutaneous mass of his right thigh that was previously undetected on prenatal imaging. He was found to have severe thrombocytopenia and a grade IV intraventricular hemorrhage. His lesion enlarged rapidly and he was diagnosed with KHE complicated by KMP.

Treatment: Currently a standardized treatment algorithm has not been established for KHE with KMP. A consensus in 2013 proposed vincristine with systemic steroids as first line treatment. Case reports since that time have presented favorable data for considering sirolimus therapy first. Given the rapid clinical deterioration of our patient, he was quickly initiated on systemic therapy with sirolimus. His vascular anomaly responded favorably to this treatment with a marked involution of the mass and improved function of the affected extremity after 4 weeks of therapy. Another critical aspect of his care was consultation to hematology for appropriate parameters for frequent transfusions and supportive care. Sirolimus is thought to be effective by stopping lymphangiogenesis. Additional data is needed in determining a step-wise treatment algorithm for KHE.

References:

1) Hammill AM, Wentzel M, Gupta A, Nelson S, Lucky A, Elluru R, Dasgupta R, Azizkhan RG, Adams DM. Sirolimus for the treatment of complicated vascular anomalies in children. Pediatr Blood Cancer. 2011 Dec;57(6):1018-24. Epub 2011 Mar 28.
2) Rodriguez V, Lee A, Witman PM, Anderson PA. Kasabach-merritt phenomenon: case series and retrospective review of the mayo clinic experience. J Pediatr Hematol Oncol. 2009 Jul;31(7):522-6.
3) Adams DM, Trenor CC 3rd, Hammill AM, Vinks AA, Patel MN, Chaudry G, Wentzel MS, Mobberley-Schuman PS, Campbell LM, Brookbank C, Gupta A, Chute C, Eile J, McKenna J, Merrow AC, Fei L, Hornung L, Seid M, Dasgupta AR, Dickie BH, Elluru RG, Lucky AW, Weiss B, Azizkhan RG. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. Pediatrics. 2016 Feb;137(2):e20153257. Epub 2016 Jan 18.
4) Blatt J, Stavas J, Moats-Staats B, Woosley J, Morrell DS. Treatment of childhood kaposiform hemangioendothelioma with sirolimus. Pediatr Blood Cancer. 2010;55(7):1396.
5) Wang Z, Li K, Dong K, Xiao X, Zheng S. Successful treatment of Kasabach-Merritt phenomenon arising from Kaposiform hemangioendothelioma by sirolimus. J Pediatr Hematol Oncol. 2015;37(1):72.
6) Jahnel J, Lackner H, Reiterer F, Urlesberger B, Urban C. Kaposiform hemangioendothelioma with Kasabach-Merritt phenomenon: from vincristine to sirolimus. Klin Padiatr. 2012 Oct;224(6):395-7. Epub 2012 Oct 15.
7) Fernandes VM, Fargo JH, Saini S, et al. Kaposiform lymphangiomatosis: unifying features of a heterogeneous disorder. Pediatr Blood Cancer 2015; 62:901.
8) Lackner H, Karastaneva A, Schwinger W, et al. Sirolimus for the treatment of children with various complicated vascular anomalies. Eur J Pediatr 2015; 174:1579.
9) Uno T, Ito S, Nakazawa A, et al. Successful treatment of Kaposiform hemangioendothelioma with everolimus. Pediatr Blood Cancer 2015; 62:536.
10) Lacobas I, Simon ML, Amir T, et al. Decreased vascularization of retroperitoneal kaposiform hemangioendothelioma induced by treatment with sirolimus explains relief of symptoms. Clin Imaging 2015; 39:529.
11) Nadal M, Giraudeau B, Tavernier E, et al. Efficacy and Safety of Mammalian Target of Rapamycin Inhibitors in Vascular Anomalies: A Systematic Review. Acta Derm Venereol 2016; 96:448.
12) Wang H, Duan Y, Gao Y, Guo X. Sirolimus for Vincristine-Resistant Kasabach-Merritt Phenomenon: Report of Eight Patients. Pediatr Dermatol 2017; 34:261.

Case #13 – A Baffling Bilateral Lower Extremity Rash

Presenters: Ramya Vangipuram, MD, Richard Jahan-Tigh, MD

HPI: 53-year-old Hispanic woman with pulmonary tuberculosis admitted to the hospital with two-week history of progressive painful rash on the bilateral lower extremities. Notes fever, joint pain, and swelling.

PMH: TB associated choroiditis, hepatitis C

Medications: Rifampin, isoniazid, pyrazinamide, ethambutol

Physical Exam: Few 6-12 mm well demarcated violaceous papules and plaques with central pustulation on the lower thighs, shins, and calves.

Case #13 – A Baffling Bilateral Lower Extremity Rash

Diagnosis: Erythema induratum of Bazin

Histopathology: Small and medium vessel leukocytoclastic vasculitis with lobular and septal panniculitis. Negative AFB, fungal, and bacterial cultures.

Discussion: Erythema induratum of Bazin is a tuberculid, which is characterized as a hypersensitivity reaction to *Mycobacterium tuberculosis* (TB) antigens. Other tuberculids include papulonecrotic tuberculid and lichen scrofulosorum. Tuberculid reactions are negative for cutaneous mycobacterial infection. Erythema induratum occurs in less than 1% of patients with TB. It is more commonly seen in women and presents with recurrent violaceous nodules with a propensity for ulceration. Panniculitis and vasculitis are typical histopathological findings. This condition tends to improve with treatment of underlying tuberculosis.

Treatment: Topical high potency steroids and oral steroids for symptomatic relief

References:

1) Magalhaes TS, Dammert VG, Samorano LP, et al. Erythema induratum of Bazin: Epidemiological, clinical and laboratorial profile of 54 patients. J Dermatol. 2018;45(5):628-9.
2) Connors WJ, Fisher DA, Kunimoto DY, et al. Program-wide review and follow-up of erythema Induratum of Bazin and tuberculosis-associated ocular inflammation management in a TB low-incidence setting: need for improved treatment candidate selection, therapy standardization, and care collaboration. BMC Infect Dis. 2019; 19(1):97.

Case #14 – Tattoo Snafu

Presenters: Helena Jenkinson, MD, Richard Jahan-Tigh, MD

HPI: A 33-year-old man presents with 4-month history of worsening skin lesions on face, trunk, and extremities

PMH: Sarcoidosis

Medications: Prednisone 40 mg daily, azathioprine 150 mg daily, hydroxychloroquine 200 mg twice daily, doxycycline 100 mg twice daily, amlodipine 10 mg daily

Physical Exam: Patient has crusted ulcers with surrounding erythema on the right temple, right upper back, bilateral arms, and bilateral legs. He has scaly plaques confined within areas of tattoos on his arms, chest, and abdomen.

Case #14 – Tattoo Snafu

Diagnosis: *Mycobacterium haemophilum*

Histopathology: Biopsy shows mild hyperkeratosis and acanthosis of the epidermis with underlying perivascular inflammation and abundant noncaseating granulomas. PAS stain is negative for fungal organisms. AFB and Fite stains show rare small rods.

Discussion: *Mycobacterium haemophilum* was first identified as a pathogen in 1978. Since then, infections have been reported in more than 100 patients. Infections have been most frequently reported in the severely immunocompromised, but it may also cause lymphadenitis in healthy children.

Cutaneous infections typically present as erythematous papules, plaques, or nodules that may ulcerate. Cutaneous lesions occur most frequently on the arms and legs, especially overlying joints. *M. haemophilum* is slow-growing and grows optimally at 30-32°C, a lower temperature than most other pathogenic mycobacteria.

Treatment: After being admitted, the patient was initially started on clarithromycin, moxifloxicin, and cefoxitin. This was changed 1 month later when patient developed fever again to clarithromycin, isoniazid, rifampin, and ethambutol with significant improvement of skin lesions. Patient was switched to azithromycin, linezolid, and rifampin after receipt of PCR results and discussion with outside mycobacterium specialist.

Skin biopsies repeated at several month intervals throughout the course of treatment continued to show AFB organisms. As of 22 months after diagnosis, skin biopsy was still positive, but with fewer organisms. Patient has since been lost to follow-up.

References:

1) Elsayed S, Read R. Mycobacterium haemophilum osteomyelitis: case report and review of the literature. BMC Infect Dis. 2006;6:70.
2) Lindeboom JA, Bruijnesteijn van Coppenraet LE, van Soolingen D, Prins JM, Kuijper EJ. Clinical manifestations, diagnosis, and treatment of Mycobacterium haemophilum infections. Clin Microbiol Rev. 2011;24(4):701–717.

Case #15 – A Newly Noxious & Necrotic Abdomen

Presenters: Allison Pye, MD, Hung Doan, MD, PhD

HPI: A 27-year-old African American woman presented to the emergency department with a two-week history of retiform purpura on the bilateral flanks that began as bruising one day after she underwent "traditional liposuction" in Miami, Florida. The lesions were associated with fevers and chills.

PMH/PSH: No history of blood clots or abnormal bleeding. History of liposuction and breast reduction in Oklahoma in 2014 without complications.

FH: No hematologic or clotting disorders.

Physical Exam: Bilateral flanks with symmetrical, deeply violaceous, non-tender indurated plaques with sharply demarcated, angulated, erythematous borders. Occasional overlying flaccid and ruptured bullae.

Case #15 – A Newly Noxious & Necrotic Abdomen

Diagnosis: Liposuction-induced necrosis

Treatment: Aggressive wound care in burn unit, incision and drainage, subsequent debridement of necrotic tissue followed by split-thickness skin grafts by plastic surgery

Discussion: Liposuction is one of the most commonly performed cosmetic procedures in the world, and an estimated 300,000-400,000 procedures are performed annually in the United States. The advent of tumescent anesthesia allows the procedure to be performed in an outpatient setting under local anesthesia with minimal blood loss, thereby increasing the safety and accessibility of the procedure. Common sequelae such as swelling, numbness, bruising, and erythema at incision sites must be differentiated from complications, which include infection, hematomas, seromas, and skin necrosis. Systemic complications may include significant blood loss, hypothermia, visceral perforation, fulminant infection, fat embolism syndrome, deep venous thrombosis, and pulmonary edema.

Bruising and ecchymosis are expected to occur after the procedure, peak around the first week, and resolve 2-4 weeks postoperatively. Chronic smoking or coagulation abnormalities may contribute to more severe or persistent ecchymoses; however, damage to superficial veins during the procedure can lead to serious complications. Superficial liposuction may damage the subdermal vascular plexus leading to full-thickness skin necrosis, which we observed in our patient. Other causes of skin necrosis include the use of sharp cannulas or aggressive liposuction of the abdomen (large volumes >5L). Treatment of liposuction-induced skin necrosis is largely supportive and depends on the extent of body surface area involvement and clinical presentation.

During her hospitalization, our patient revealed that she underwent aggressive, large volume (13-14L) superficial liposuction with a plastic surgeon in Columbia, rather than in Miami as she originally reported. “Lipotourism,” a recent trend over the past two decades, involves foreign physicians offering lower rates to patients willing to travel overseas for surgery. The increasing popularity and availability of cosmetic procedures, often offered by inexperienced providers or lay persons, substantiates our duty as physicians and dermatologists to inform patients of the risks associated with such procedures and benefits of pursuing care with adequately trained and experienced providers.

References:

1) Coleman, W, Flynn, T, Coleman, K. Liposuction. In: Bolognia J, Jorizzo JL, Schaffer JV, eds. Dermatology. 3rd ed. Mosby Elsevier; 2012.
2) Dixit VV, Wagh MS. Unfavourable outcomes of liposuction and their management. Indian J Plast Surg. 2013;46(2):377–392.
3) Corderi, V. Plastic surgery tourism? Dangers of going under the knife on the cheap. http://www.nbcnews.com/id/7222253/ns/dateline_nbc/t/plastic-surgery-tourism/#.XZQbklDato5. March 18, 2005. Accessed October 1, 2019.

Case #16 - Violaceous Changes on Breast after Treatment for Breast Cancer

Presenters: Chen Yao, MD, Kelly Nelson, MD

HPI: 55-year-old female with stage T1bN0M0 invasive ductal carcinoma of the right breast on anastrozole who presents with six months of violaceous macules and papules of the right breast.

PMH: Right breast cancer: diagnosed 2014, prior treatments included breast segmental mastectomy, 12 cycles adjuvant paclitaxel, 4 cycles doxorubicin/cyclophosphamide and a course of radiation therapy to the right breast, completed in 4/2015.

PSH: Right breast segmental mastectomy, total abdominal hysterectomy with bilateral salpingo-ophorectomy

Medications: Anastrozole 1mg tablet daily

Physical Exam: Violaceous macules coalescing into a confluent patch with 2-3 small raised papules with slight peau d'orange textural changes on the right medial to inferior breast. The left breast and remainder of the right breast are within normal limits with no erythema or nodularity.

Case #16 - Violaceous Changes on Breast after Treatment for Breast Cancer

Diagnosis: Radiation-induced angiosarcoma of the breast (RAIS)

Histopathology: H&E from 4 separate sites showed irregular anastomosing vessels lined by endothelial cells showing nuclear atypia involving the superficial and mid-dermis, with no necrosis identified.

Discussion: Radiation therapy is an essential adjuvant treatment in early stage breast cancer, used to decrease the risk of local breast cancer recurrence. Unfortunately, the development of a second primary tumor is a rare late complication. Radiation-induced angiosarcoma (RAIS) of the breast usually arises on the previously irradiated skin several years after radiotherapy and presents as painless multifocal erythematous patches or plaques similar to a hematoma. Overall incidence rate of RAIS varies between 0.002% and 0.050% per year, with cumulative incidence of 0.09% fifteen years after initial dose of radiotherapy. Cutaneous biopsy is essential for the diagnosis, which shows irregular anastomosing vessels lined by endothelial cells showing nuclear atypia. RAIS can occur beyond the conventional 5 year oncological follow up, thus long term follow-up is necessary with attention to post-irradiation skin lesions to ensure early detection and prompt therapeutic intervention.

Treatment: Treatment of RAIS is primarily surgical, and mastectomy with negative margins is considered the standard procedure. Unfortunately, recurrences are common and an approach combining surgery, chemo-, and radiotherapy may be more effective but remains ambiguous. In this case, the patient was referred to sarcoma medical oncology and was enrolled in a pilot study of Oraxol, which is comprised of oral paclitaxel and a novel P-glycoprotein inhibitor.

References:

1) Bonito FJP, de Almeida Cerejeira D, Dahlstedt-Ferreira C, et al. Radiation-induced Angiosarcoma of the breast: A review. Breast J. 2019 Aug 25.
2) Amajoud Z, Vertongen AS, Wetens R, et al. Radiation induced Angiosarcoma of the breast: case series and review of the literature. Facts Views Vis Obgyn. 2018 Dec;10(4):215-220.
3) Ronen S, Ivan D, Torres-Cabala CA, et al. Post-radiation vascular lesions of the breast. J Cutan Pathol. 2019 Jan;46(1):52-58. Pub 2018 Nov 4.
4) Wei NJJ, Crowley TP, Ragbir M. Early breast Angiosarcoma development after radiotherapy: a cautionary tale. Ann Plast Sure. 2019 Aug;83(2):152-153.

Case #17 – Vesicular Eruption in a Patient with Urothelial Cancer

Presenters: Taylor Duke, MD, Sharon Hymes, MD

HPI: 68-year-old African American male with urothelial cancer presents with pruritus and short-lived vesicles located on the trunk and extremities for 3 months.

PMH: Urothelial carcinoma with neuroendocrine differentiation, type II diabetes mellitus

FH: Lynch syndrome

Medications: Nivolumab, gabapentin, valacyclovir

Physical Exam: Fitzpatrick skin type IV. On the chest, upper arms, dorsal arms, thighs and lower legs there are hypopigmented 5-6 mm round scars with rim of hyperpigmentation; some with pink center and some more erythematous with a collarette of scale. On the left mid shin there is a tense vesicle.

Case #17 – Vesicular Eruption in a Patient with Urothelial Cancer

Diagnosis: Nivolumab-induced bullous pemphigoid

Histopathology: Microscopic examination of biopsies obtained from the lesion on the shin demonstrated a subepidermal blister with associated perivascular dermatitis with eosinophils. PAS stain did not detect fungal organisms.

Perilesional direct immunofluorescence (DIF) showed IgG and C3 deposition in a linear pattern along the dermoepidermal junction (DEJ).

Discussion: Nivolomab is a human monoclonal antibody against programmed cell death protein-1 (PD-1). It functions as a checkpoint inhibitor and is increasingly used in the treatment of many types of cancer. Cutaneous immune-related adverse events (irAEs) are among the most common adverse events in patients on immunotherapy.

Bullous pemphigoid is a subepidermal autoimmune blistering condition driven by autoantibody production against hemidesmosomal structural proteins BP180 and BP230. PD-1/PD-L1 inhibitor-induced bullous pemphigoid is a rare but potentially serious dermatologic toxicity. Diagnosis is typically made by skin biopsy and serologic studies.

Treatment: Treatment for immunotherapy induced bullous pemphigoid varies and there is no specific algorithm to guide treatment. Therefore, conventional therapies can be considered. It is often necessary to hold immunotherapy to prevent further progression of BP lesions. Our patient was treated with topical and oral corticosteroids without improvement. His immunotherapy was stopped and he received two doses of rituximab with improvement in his disease and decrease in his BP antigen levels.

References:

1) Puzanov I, Diab A, Abdallah K et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95.
2) Lopez Adriana T., Geskin Larisa. A Case of Nivolumab-Induced Bullous Pemphigoid: Review of Dermatologic Toxicity Associated with Programmed Cell Death Protein-1/Programmed Death Ligand-1 Inhibitors and Recommendations for Diagnosis and Management. The Oncologist. 2018;23(10):1119–1126.
3) Yoest JM. Clinical features, predictive correlates, and pathophysiology of immune-related adverse events in immune checkpoint inhibitor treatments in cancer: A short review. Immunotargets Ther. 2017;6:73–82.
4) Sowerby L, Dewan AK, Granter S et al. Rituximab treatment of nivolumab-induced bullous pemphigoid. JAMA Dermatol. 2017;153:603–605.

Case #18 - Is it Just Woolly Hair?

Presenters: Yamila Goenaga Vázquez, MD, Adelaide A. Hebert, MD

HPI: A four-year old healthy female presents with abnormal curly hair on the lower posterior scalp recently noted by her mother. She has been using different over the counter shampoos and vitamins without success. No other family members with similar symptoms.

ROS: No other cutaneous or nail abnormalities.

Physical exam: Posterior scalp and hair: localized area of unruly hair surrounded by straight hair in frontal and parietal scalp

Case #18 - Is it Just Woolly Hair?

Diagnosis: Woolly hair nevus

Discussion: Woolly hair refers to a group of congenital hair shaft disorders, characterized by tightly fine and coiled hair of rough texture but no associated fragility. Diagnosis is clinical. It has been classified by mode of inheritance (autosomal dominant, autosomal recessive, non-heritable) and distribution (localized, diffused). Woolly hair has been associated with abnormalities of eyes, heart, and teeth as well as malignant disorders.

When woolly hair presents as one circumscribed lesion, it is called woolly hair nevus. This form is non-heritable and appears within the first 2 years of life. It can be associated with verrucous epidermal nevus in 50% of the cases and is considered benign. However, these clinical manifestations are also present in patients with Costello Syndrome, inherited in an autosomal dominant fashion, and caused by a mutation in HRAS. These patients are at higher risk of carcinogenesis, most commonly rhabdomyosarcoma of abdomen and pelvis (15% of patients) that appear by 2 years up to 20 years of age. On the other hand, when woolly hair presents in the diffuse form, it can be associated with palmoplantar keratoderma and arrhythmogenic cardiomyopathy, termed the cardiocutaneous phenothype, which includes Naxos Disease and Carvajal Syndrome. In these patients, the cardiac manifestations can be clinically silent until after the 2nd decade of life and present with sudden cardiac death.

The dermatologic features of patients with woolly hair can provide a clue as to whether it is part of a syndrome or an isolated entity. A thorough dermatological examination as well as labs, echocardiogram, ECG, abdominal ultrasound, and ophthalmological evaluations are recommended for all patients presenting with woolly hair. Some may require periodic screening for carcinogenesis, genetic evaluation, or serial cardiac work up, even in the absence of overt symptoms.

Treatment: The patient was advised to avoid physical and chemical traumatic measures.

References:

1) Taylor AE. Hereditary woolly hair with ocular involvement. Br J Dermatol. 1990;123:523–5.
2) Baykan A, Olgar S, Argun M, Ozyurt A, Pamukcu O, Uzum K, Narin N. Different clinical presentations of Naxos disease and Carvajal syndrome: Case series from a single tertiary center and review of the literature. The Anatolian Journal of Cardiology, 2015; 15(5).
3) Maruthappu T, Posafalvi A, Castelletti S, Delaney PJ, Syrris P, O'Toole EA, Kelsell DP. Loss of function desmoplakin I and II mutations underlie dominant arrhythmogenic cardiomyopathy with a hair and skin phenotype. British Journal of Dermatology. 2018;2(10)55-58.
4) Nishihara K, Tohyama M, Kubo A. A case of woolly hair nevus, multiple linear pigmentation, and epidermal nevi with somatic HRAS p.G12S mutation. Pediatric Dermatology, 2019; 92(5):163-65.

Case #19 – The Persistent Papules

Presenters: Mary Alice Sallman, MD, Adelaide A. Hebert, MD, Megan Rogge, MD

HPI: 21-year-old African American male presents with persistent papules located on the face, inner arms and above the knees on the thighs for five years, previously diagnosed as molluscum contagiosum unresponsive to cryotherapy treatment.

PMH: Port wine stain of the chest, venous malformations of the bilateral lower extremities, congenital pigment alteration of the trunk, limb hemi-hypertrophy

PSH: Growth plate surgery bilateral lower extremities 2012; hernia repair 2007

FH: Grandfather with port-wine stain and atopic dermatitis

Medications: Aspirin 81 mg daily

Physical Exam: White to clear-colored, flat-topped papules in clusters located on the medial canthi bilaterally as well as the inner left upper extremity and bilateral lower extremities above the knees. In addition, patient had a dark red well-demarcated patch on the left chest overlying a macular area of hyperpigmentation. An additional dark red patch was located on the right mid back and flank. On the right chest, an irregularly shaped brown patch extended on to the back. On the back a well-demarcated brown patch stopped abruptly at the midline with stuck-on dark brown papules and areas of hypertrichosis. From the knees down on the lower extremity were dilated, palpable vessels that were more prominent on the right than the left lower leg. Additionally, there was right lower limb hypertrophy compared to the left lower extremity.

Case #19 – The Persistent Papules

Diagnosis: Lymphangiomas in the setting of phakomatosis pigmentovascularis type Ib with Klippel Trenaunay syndrome (KTS)

Histopathology: Microscopic examination of biopsy from one of the white-clear clustered papules of the left distal thigh above the knee demonstrated a thin vascular lumina impinging upon the epidermis, consistent with proliferation and dilation of lymph vessels in the papillary dermis.

Discussion: Phakomatosis pigmentovascularis (PPV) is a rare syndrome characterized by vascular malformations and pigmentary anomalies. The pigmented lesions include epidermal nevi, dermal melanocytosis, nevus spilus (macular type), and café-au-lait macules while the vascular malformations include port-wine stain, capillary malformations, and cutis marmorata telangiectatica congenita. PPV is subtyped I-V depending on the types of pigmented lesions that are present. The subtype 'a' designation is given when only cutaneous features are present. The type 'b' designation is given when there are extracutaneous abnormalities present such as melanosis oculi, Sturge-Weber, KTS, or nevus of Ota.

The clinical findings manifested in our patient including a port-wine stain and a linear epidermal nevus met the criteria for a diagnosis of PPV type I. The triad of cutaneous vascular malformations (lymphangiomas), venous varicosities, and hypertrophy of soft tissues establishes a diagnosis of Klippel Trenaunay Syndrome which is also an extracutaneous PPV association (and gives the patient the subtype 'b' designation). Therefore, this patient was given the diagnosis of PPV type Ib with KTS.

Treatment: After diagnosis of PPV Type Ib with Klippel Trenauny Syndrome, the patient was referred to the Memorial Hermann Vascular Anomalies Clinic. Biopsies of skin tissue were sampled for genetic analysis. At this time, the patient is due to undergo MRI of bilateral lower extremities to be shared with interventional radiology in order to assess need for repairing vascular malformations of the lower extremities. While awaiting possible intervention, he will continue taking daily aspirin.

References:

1) Fernández-Guarino M, Boixeda P, de las Heras E, Aboin S, García-Millán C , Olasolo PJ. Phakomatosis pigmentovascularis: Clinical findings in 15 patients and review of the literature. Journal of the American Academy of Dermatology 2008;58:88-93.
2) Vidaurri-de la Cruz H, et al. Phakomatosis pigmentovascularis II A and II B: clinical findings in 24 patients. The Journal of dermatology 2003;30:381-8.
3) Happle R. Loss of heterozygosity in human skin. J Am Acad Dermatol 1999;41:143-64.
4) Joshi A, Garg VK, Agrawal S, Agarwalla A , Thakur A. Port-Wine-Stain (Nevus Flammeus), Congenital Becker's Nevus, Café-au-lait-Macule and Lentigines: Phakomatosis Pigmentovascularis Type Ia—A New Combination. The Journal of dermatology 1999;26:834-6.
5) Rapini RP. Practical dermatopathology. Philadelphia: Elsevier Mosby, 2005.
6) Bolognia, Jean, Joseph L. Jorizzo, and Julie V. Schaffer. Dermatology. Philadelphia: Elsevier Saunders, 2017.

Case #20 –An Uninvited Guest

Presenters: Sampreet Reddy, MD, Steven R. Mays, MD

HPI: 40 year old HIV+ male from Honduras presents with a one year history of a widespread, itchy rash.

PMH: HIV (CD4 count 61) on abacavir-dolutegravir-lamivudine.
History of oral histoplasmosis made by biopsy in 2016; urine antigen negative; s/p 1 year of oral itraconazole.
History of syphilis, most recently treated with benzathine penicillin 2.4M IU IM once weekly for 3 weeks 10 months prior to presentation.

Medications: Abacavir-dolutegravir-lamivudine 600mg-50mg-300mg QD
Trimethoprim-sulfamethoxazole 160mg-400mg QD
Itraconazole 200mg QD

Physical Exam: Widespread erythematous macules and patches on the neck, trunk, and bilateral upper and lower extremities. Oral mucosa and nasal mucosa are normal

Labs: Eosinophilia of 10.2 %
CD4 count of 61

Histopathology: Diffuse infiltration of the dermis by thousands of 2-3 micron microorganisms many of which are present within histiocytes, but some which are free within the dermis. The organisms are positive for Giemsa and CD1a. Staining for PAS and AFB are negative.

Case #20 –An Uninvited Guest

Diagnosis: Diffuse cutaneous leishmaniasis

Discussion: Leishmaniasis is a spectrum of infections caused by the flagellated protozoans, *Leishmania,* and spread by the bite of female sandflies. The clinical variants of leishmaniasis include cutaneous, mucocutaneous, diffuse cutaneous, and visceral disease. Cutaneous leishmaniasis may be of the New World or the Old World variant, based on sub-species and geographic location.

Additional skin biopsies from this patient were sent to the CDC; PCR confirmed leishmaniasis (*L. donovoni* complex*).* The subspecies is likely *L. infantum chagasi* based on geographic distribution. While this New World subspecies usually causes visceral leishmaniasis, it can also cause cutaneous leishmaniasis.

Two years prior to his skin disease, the patient had a large oral ulcer, histology of which suggested histoplasmosis; this may have *actually* been an early manifestation of leishmaniasis. Cultures, serum, and urine antigen tests for histoplasmosis were negative at that time. On pathology, histoplasmosis may closely resemble leishmaniasis; both present as parasitized histiocytes containing organisms measuring 2-4 microns. Leishmaniasis can be identified by its kinetoplast, a <1 micron paranuclear organelle, as well as by the "Marquee Sign," the distribution of parasites at the periphery of a cell, like the light bulbs of a marquee sign. These features may, however, be difficult to appreciate. The CD1a stain may help to confirm the diagnosis of Leishmaniasis.

Treatment: The patient was treated with 5 days of liposomal amphotericin B followed by 5 additional weekly doses. The patient's rash and pruritus improved following treatment.

References:

1) Bolognia J, Jorizzo JL, Rapini RP. Dermatology. 4nd ed. St. Louis: Mosby Elsevier, 2008. Rapini RP. Practical dermatopathology. Philadelphia: Elsevier Mosby, 2017.
2) Fernandez-Flores A, Rodriguez-Peralto JL. Morphological and immunohistochemical clues for the diagnosis of cutaneous leishmaniasis and the interpretation of CD1a status. J Am Acad Dermatol. 2016;74:536–543
3) Sundharkrishnan L, North JP. Histopathologic features of cutaneous leishmaniasis and use of CD1a staining for amastigotes in Old World and New World leishmaniasis. J Cutan Pathol. 2017;44:1005–1011

Case #21 – Out of the Woods?

Presenters: Ravi C. Patel, MD, Richard Jahan-Tigh, MD, MS

HPI: 36-year-old African American woman presents with generalized pruritic and blistering rash for 2 weeks. Patient went hiking 2 days prior to onset.

PMH: None

Medications: Recent dose of intramuscular penicillin

Physical Exam: Erythematous macules and papules coalescing into patches and plaques with scattered erosions and heme crusts involving the trunk, extremities, face, and neck. External lips with heme-crusted plaques.

Case #21 – Out of the Woods?

Diagnosis: Rowell syndrome

Histopathology: H&E sections showed interface dermatitis consistent with lupus erythematosus. There was parakeratosis with necrotic keratinocytes. In some areas the necrosis nearly reached full thickness. The inflammatory infiltrate was comprised mostly of lymphocytes with scattered neutrophils and extravasated erythrocytes.

Perilesional direct immunofluorescence (DIF) showed nonspecific granular IF along the basement membrane zone with multiple antibodies.

Discussion: Rowell syndrome is a rare subtype of lupus erythematosus (LE) characterized by erythema multiforme (EM)-like lesions. It presents with raised typical and/or atypical targets of EM. The targets may appear with a dusky center or blister. On histopathology, Rowell syndrome may appear similar to EM, showing necrotic keratinocytes, blister formation, and perivascular lymphocytic infiltration. Changes of lupus such as interface dermatitis and mucin deposition are often appreciated.

Rowell syndrome was characterized in 1963 by Rowell et al. They reported a syndrome characterized by LE, EM-like lesions, and immunologic abnormalities in the serum (anti-La antibody, speckled antinuclear antibody, or positive rheumatoid factor). Many similar cases have been reported since, but some do not strictly adhere to the original description.

In 2000, Zeitouni et al. proposed a modified version of the original criteria, which requires 3 major and 1 minor criterion to be met for diagnosis. Major criteria include: (1) systemic lupus erythematosus, discoid LE, or subacute cutaneous LE; (2) EM-like lesions (with or without involvement of the mucous membranes); and (3) speckled pattern of antinuclear antibody. Minor criteria include: (1) chilblains; (2) anti-Ro antibody or anti-La antibody; and (3) positive rheumatoid factor.

Treatment: As previously noted, Rowell syndrome may represent a severe variant of acute or subacute cutaneous lupus erythematosus. Thus, treatment should be similar to these entities. Sun protection is a vital part of all therapeutic regimens; topical steroids can be adjunct to this. Additionally, systemic therapy is usually needed. Anti-malarials such as hydroxychloroquine remain the gold standard for first line therapy. The response to antimalarials is relatively slow, with a minimum of 2-3 months for efficacy to be appreciated. Thus, corticosteroids (0.5 to 1 mg/kg/day of prednisone equivalent) and other fast acting immunosuppressive medications are necessary.

Our patient was managed in conjunction with rheumatology and was started on a regimen of prednisone 60 mg daily, hydroxychloroquine 200 mg BID, and cyclosporine 200 mg BID.

References:

1) Bolognia J, Jorizzo JL, Rapini RP. Dermatology. 4th ed. St. Louis: Mosby Elsevier, 2017.
2) Zeitouni NC, Funaro D, Cloutier RA, Gagné E, Claveau J. Redefining Rowell's syndrome. Br J Dermatol. 2000;142:343–6
3) Rowell NR, Beck JS, Anderson JR. Lupus erythematosus and erythema multiforme-like lesions. A syndrome with characteristic immunological abnormalities. Arch Dermatol. 1963;88.

Case #22 – Multiplying Nodules

Presenters: Saisindhu Narala, MD, Jaime Tschen, MD, Richard Jahan-Tigh, MD, MS

HPI: 59 year-old male with no past medical history presents for evaluation of bumps on his left hand. He had a cyst excised from the left dorsal hand and two months later noticed a red bump near the incision site. Over the course of one month, he developed two new red bumps proximally, all asymptomatic. His social history was only remarkable for frequent gardening and tending to his outdoor fountain.

Physical Exam: Left dorsal thumb had three erythematous nodules in a sporotrichoid pattern with minimal superficial scale.

Histopathology: H&E from biopsy of the left hand revealed diffuse granulomatous inflammation in the dermis with round to ovoid basophilic bodies. PAS stain revealed spherical morula-like sporangia.

Case #22 – Multiplying Nodules

Diagnosis: Cutaneous protothecosis

Discussion: *Prototheca* are achlorophyllic algae that rarely cause human infection. When they do, they cause cutaneous (66%), olecranon bursa (15%) and systemic (19%) infection. The *Prototheca wickerhamii* and *Prototheca zopfii* species have been shown to cause human disease. These algae are ubiquitous in the environment, and typical sources include trees, grass, fresh water and saltwater, wastewater, and animals such as cattle, deer, and dogs. Direct inoculation by trauma is the most commonly implicated method of infection, and infection typically presents on the extremities for this reason. Greater than 50% of infections occur in immunosuppressed patients. Occupational exposure is an important risk factor for immunocompetent patients. These include farming, fishing, handling raw seafood, and working in an aquarium. The infection is typically indolent, presenting as eczematous patches, plaques, nodules, or ulcers.

Diagnosis can be via histopathologic examination or culture. The organisms range from 3-30 micrometers in size and consist of sporangia with thick, double-layered walls filled with multiple endospores. The unique appearance of the endospores helps differentiate it from other deep fungal infections such as coccidioidomycosis, blastomycosis, paracoccidioidomycosis, and cryptococcosis.

Treatment: There is no gold standard for treatment of cutaneous protothecosis due to the rarity of the disease. Most reported cases have been treated with amphotericin B, fluconazole, voriconazole, and itraconazole, with treatments ranging from two weeks to six months. Excision has also been effective in few case reports. Our patient was treated with terbinafine 250 mg daily for four weeks with significant improvement.

References:

1) Tseng HC, Chen CB, Ho JC, et al. Clinicopathological features and course of cutaneous protothecosis. J Eur Acad Dermatol Venereol. 2018 Sep;32(9):1575-1583.
2) Tan M, Pan JY, Chia HY, and Oon HH. Cutaneous protothecosis on the bilateral wrists of a food handler. Clin Exp Dermatol. 2017 Jan;42(1):72-74.
3) Jenkinson H, Thelin L, McAndrew R, et al. Cutaneous protothecosis in a patient on ustekinumab for psoriasis. Int J Dermatol. 2018 Oct;57(10):1246-1248.
4) Woo JY, Suhng EA, Byun JY, Choi HY, Sung SH, and Choi YW. A Case of Cutaneous Protothecosis in an Immunocompetent Patient. Ann Dermatol. 2016 Apr;28(2):273-274.
5) Wang F, Feng P, Lin Y, et al. Human Cutaneous Protothecosis: A Case Report and Review of Cases from Mainland China, Hong Kong, and Taiwan. Mycopathologia. 2018 Oct;183(5):821-828.
6) Fong K, Tee SI, Ho MS, and Pan JY. Cutaneous protothecosis in a patient with previously undiagnosed HIV infection.