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Chicago Dermatological Society

PROTOCOL BOOK
December 14, 2022

Co-hosted by University of Chicago - Department of Dermatology

Guest Speaker: Ashfaq A. Marghoob, MD

Director of Clinical Dermatology at Memorial Sloan Kettering Cancer Center Hauppauge

Board-Certified Dermatologist Specializing in the Diagnosis and Treatment of Cancers of the Skin.

Program

Co-hosted by University of Chicago - Department of Dermatology

Wednesday, December 14, 2022
University of Chicago Gleacher Center
Chicago, Illinois

8:00 a.m. **Registration & Continental Breakfast with Exhibitors**

8:30 a.m. - 10:15 a.m. **Clinical Rounds**
Slide viewing/posters – ongoing through the early morning

9:00 a.m. **Welcome and Opening Comments**
Joerg Albrecht, MD PhD - CDS President

9:00 a.m. - 10:00 a.m. **Morning Lecture**
"The Role of Dermoscopy in Melanoma Detection: the Yin-Yang"
Ashfaq A. Marghoob, MD

10:00 a.m. - 10:30 a.m. **Break and Visit with Exhibitors**

10:30 a.m. - 12:00 p.m. **Resident Case Presentations & Discussion**

12:00 p.m. - 12:30 p.m. **Box Lunches & Visit with Exhibitors**

12:30 p.m - 1:15 p.m. **CDS Business Meeting**

1:15 p.m. - 2:15 p.m. **Afternoon Lecture**
"Melanoma Specific Structures"
Resident Lecture

Program adjourns

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Liesl Schroedl, MD, Oluwakemi Onajin, MD, Christopher R. Shea, MD, Diana Bolotin, MD, PhD, Arlene Ruiz de Luzuriaga MD, MPH, MBA

HISTORY OF PRESENT ILLNESS

An 86-year-old woman presented with an irregular brown patch on the left cheek that had been present for one year. She stated that the lesion had been gradually enlarging over time but was otherwise asymptomatic.

PAST MEDICAL HISTORY

Left breast invasive ductal carcinoma s/p lumpectomy and radiation, hypertension, osteoarthritis, migraines, cataracts, allergic rhinitis

MEDICATIONS

Alprazolam, amlodipine, aspirin, cetirizine, ergocalciferol, fluticasone, hydrochlorothiazide

ALLERGIES

Peanut, penicillin (hives), sulfonamides (pruritus), latex (burning sensation)

FAMILY HISTORY

No family history of melanoma or solid-organ malignancy.

SOCIAL HISTORY

No alcohol, tobacco, or illicit drug use.

PHYSICAL EXAM

The patient appeared generally well. The left cheek had a 1.1 cm x 1.4 cm light brown to dark brown variegated patch; dermoscopy demonstrated rhomboidal structures, asymmetrical follicular openings, and an annular-granular pattern.

DERMATOPATHOLOGY

Histologic sections from two separate shave biopsies, one from the anterior portion and one from the posterior portion of the lesion, demonstrated invasive malignant melanoma, superficial spreading type, Clark level II, Breslow thickness at least 0.2, with extension to the deep margin. No mitotic figures, ulceration, regression, lymphatic invasion, perineural invasion, microscopic satellitosis, or associated melanocytic nevus were identified. Tumor-infiltrating lymphocytes were non-brisk. Predominant cytology was small-cell in nature.

LABORATORY DATA

None pertinent

DIAGNOSIS

Invasive melanoma, superficial spreading type

TREATMENT AND COURSE

Given the initial diagnosis was based on a partial biopsy, a debulk specimen was sent for definitive staging with vertical sections. Histopathology revealed an invasive melanoma, superficial spreading type with a Clark level II and a Breslow thickness of 0.2mm, constituting AJCC 8 Stage T1a. The patient subsequently underwent 'slow Mohs' staged excision for margin control with complete peripheral and deep margin assessment. Histopathologic examination of the first stage of slow Mohs revealed residual malignant melanoma in situ at the 6-to-9 o'clock margin necessitating an additional stage to be performed at that margin with a final defect of 4.5cm x 2.4cm in size. Histopathologic examination of the second stage of slow Mohs revealed no residual melanocytic proliferation. The patient expressed a desire for the simplest repair, therefore the wound was repaired with a complex linear layered repair.

At follow-up three months later, the surgical site had healed well and was without nodularity or pigmentary change. The patient remains without clinical evidence of recurrence seven months post treatment.

DISCUSSION

The use of dermoscopy has revolutionized dermatologic practice by increasing diagnostic accuracy for detection of both melanoma and nonmelanoma skin cancers [1, 2]. Use of dermoscopy has allowed for earlier detection of cutaneous malignancy and has improved the malignant-to-benign biopsy ratio so that fewer biopsies of benign lesions are performed [3]. Specific dermoscopic features have been found to be helpful in distinguishing benign from potentially malignant melanocytic neoplasms. Some of these melanoma-specific structures include atypical or negative networks, atypical dots/globules, irregular blotches, streaks, crystalline structures, blue-white veil, regression structures, atypical vessels, and peripheral tan structureless areas [4]. One systematic review suggested that the features with highest specificity for melanoma included pseudopods, crystalline structures, peppering, and streaks, whereas the highest-sensitivity features included blue-white veil, atypical network, and multicomponent pattern [5]. Clearly, though, these structures will not be present in all cases; thus, it is crucial to recall that most melanomas will exhibit a deviation from normal nevus patterns as well as at least one melanoma-specific feature.

Although melanoma-specific dermoscopic structures have been identified, these features can vary topographically. Consequently, accounting for anatomic location is important when utilizing dermoscopy. Features unique to facial skin can impact the dermoscopic appearance of pigmented lesions on this anatomic location. A unique characteristic specific to facial skin is that pigmented lesions may tend to display a pseudonetwork ("annular") pattern due to decreased prominence of rete ridges on the face. This is characterized by the presence of small circles, which correlate to follicular and adnexal openings, and are found in both melanocytic lesions with a junctional component and solar lentigines. Asymmetry, color variation, and size variation in these small circles may be suggestive of malignancy. Specifically, the presence of gray dots and granules superimposed on the annular pattern is concerning for malignancy and is described as the annular-granular pattern, as was observed in our patient. Another pattern that may occur on the face is a variant of reticular pattern in which the lines appear not as a regular network but instead as fine thin lines known as fingerprinting; this occurs more commonly in solar lentigines [6].

Lentigo maligna is the most common form of melanoma that occurs on the face, and demonstrates several unique dermoscopic findings. Some of these include perifollicular granularity, asymmetric gray perifollicular openings, polygonal structures or zigzag lines, rhomboidal structures, follicle obliteration, and circle within a circle (also known as isobar pattern). A progression model has been formulated to describe the temporal sequence of dermoscopic features seen in facial lentigo maligna as it progresses toward invasion. In stage one, slate-gray dots and granules appear, which increase in concentration asymmetrically around follicles and create the annular-granular pattern. These dots and granules can develop into polygonal lines creating a zig-zag pattern and ultimately forming rhomboidal structures. As the malignancy progresses further into stage two, melanoma cells invade the follicular units in an irregular fashion and produce follicular opening asymmetry. These asymmetric follicular openings are typically characterized by a grayish color, as compared to tan or brown in the setting of lentigines. Stage three demonstrates homogeneous areas with follicular integrity maintained. The final stage of the lentigo maligna progression model is comprised of coalescent rhomboidal structures and follicular obliteration [6, 7]. Identification of any of these features should prompt biopsy, as the specific features that are observed provide an indication of how advanced the lentigo maligna has become.

While there are clear trends in dermoscopic patterns according to location and melanoma subtype, these are not entirely pathognomonic or absolute. Some of the aforementioned features of facial melanomas are not found exclusively in facial melanoma; lichenoid keratoses, pigmented actinic keratoses, and basal cell carcinomas can also display similar dermoscopic findings. Pigmented actinic keratoses can exhibit the annular-granular pattern but can be distinguished from melanoma by presence of scale or roughness and moth-eaten borders [8]. Lichenoid keratoses are thought to represent regression of a previously existing lesion, typically a lentigo; they may reveal either a diffuse granular pattern or local granular pattern, with the granules characteristically larger and coarser than those observed in melanoma. They typically also display fingerprinting; if this is absent, biopsy may be warranted. Pigmented basal cell carcinomas may also be difficult to differentiate from thick melanomas. If there is a pigment network or pseudonetwork, by definition the lesion must not be a pigmented BCC. However, if pigment network is absent, it is important to identify BCC-specific features such as arborizing vessels or gray-blue ovoid nests [9].

Herein, we present a case of invasive melanoma on the face to highlight dermoscopic features unique to facial skin. These are of significance because they help guide the decision to biopsy and may provide clues regarding melanoma progression.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #2**

PRESENTERS

Jake Lazaroff, MD, Oluwakemi Onajin, MD, Amy Xu, MD

HISTORY OF PRESENT ILLNESS

A 33-year-old female with history of B-ALL on maintenance ponatinib presented for a painful rash. The rash began in the skin folds approximately 1 year ago, about 1-2 weeks after starting treatment with ponatinib. It waxed and waned in severity throughout the year but worsened several months prior to her visit, with significant pain, burning, and tenderness to palpation. She noted diffuse

peeling and flaking all over her body, with some areas becoming so severe that they bled. She had never had a similar eruption in the past and had not tried anything for treatment. No fevers, chills, night sweats, or mucosal lesions.

PAST MEDICAL HISTORY

B-ALL (with detectable minimal residual disease on BCR-ABL PCR), migraines, renal stones, asthma

MEDICATIONS

Acyclovir, albuterol, aspirin, clonidine, dexamethasone, docusate, fluconazole, gabapentin, ponatinib

FAMILY HISTORY

None pertinent

PHYSICAL EXAM

Pink-orange plaques with follicular accentuation over the face, chest, abdomen, and back with diffuse overlying desquamative scale covering approximately 50% body surface area (BSA). The palms, soles, intertriginous zones, scalp, and oral mucosa were spared.

LABORATORY DATA

CBC with diff, CMP, hepatitis serologies, quant gold are all within normal limits

HISTOPATHOLOGY

A 4mm punch biopsy was performed. On histopathology the epidermis is acanthotic and spongiotic with hyperkeratosis and follicular plugging. There is a mild superficial perivascular lymphocytic infiltrate.

DIAGNOSIS

Pityriasis Rubra Pilaris-like Eruption to Ponatinib

TREATMENT AND COURSE

The patient was initially started on a 4-week prednisone taper starting at 40mg per day and decreasing by 10mg weekly and topical triamcinolone 0.1% ointment twice daily. At her 2-week follow up the rash continued to progress to involve nearly 70% BSA. At that time a prescription for ustekinumab was sent and the patient was started at standard dosing shortly thereafter. Additionally, in coordination with the patient's oncologist, ponatinib was held for 4 weeks. The patient's skin improved and almost completely cleared. Oncology restarted the patient on a lower dose of ponatinib shortly thereafter and the rash recurred, but was noticeably less severe. Most recently at 4-month follow up, she is no longer having pain or burning sensations but does have some residual textural changes. The current plan is to continue ustekinumab and treat her supportively while on ponatinib. Per Oncology, she will likely remain on ponatinib indefinitely given the presence of molecularly detectable residual B-ALL.

DISCUSSION

Ponatinib is an oral 3rd generation tyrosine-kinase inhibitor (TKI) that was developed for drug-resistant CML and ALL that was initially FDA approved in 2012. Unlike earlier generations of TKI's, such as imatinib, ponatinib not only inhibits BCR-ABL but also exerts broad inhibitory effects on other tyrosine kinase pathways such as fibroblast growth factor, FMS-like tyrosine kinase-3, KIT, platelet derived growth factor, vascular endothelial growth factor and the SRC families [1]. Because tyrosine kinases are important in numerous solid organ and hematologic tumors, clinical trials evaluating ponatinib for various other malignancies are ongoing [2]. As use of ponatinib becomes more common, it is important for dermatologists to be able to recognize and manage the cutaneous side effects in conjunction with the oncologic team.

It has been hypothesized that many of ponatinib's side effects are the result of its broader mechanism of action [3]. Of particular interest to dermatologists, phase I and phase II clinical trials observed cutaneous eruptions in 32% and 38% of patients [4,5]. Approximately 4% of the cutaneous adverse events were considered grade 3 or 4 [4,5]. The most common findings were a folliculocentric, keratosis pilaris-like rash, an ichthyosiform eruption, and a rash resembling pityriasis rubra pilaris (PRP)[1,6,7].

There have been several case reports and small case series of ponatinib inducing a PRP-like eruption, as was the case in our patient [6,7]. In these small cohorts the mean onset was 5 weeks after medication initiation and the mean age of onset was approximately 60 years old [6].

PRP is an inflammatory papulosquamous dermatosis that most often presents clinically with salmon-colored, follicularly based hyperkeratotic papules and plaques with islands of sparing [8]. Interestingly, in contrast to classical PRP, ponatinib induced PRP-like eruptions typically lacks palmoplantar keratoderma [6]. The histologic features of PRP include alternating horizontal and vertical ortho- and parakeratosis, or so-called checkerboarding, with a perivascular lymphocytic infiltrate in the dermis [9]. Additionally, dilated follicular openings and keratotic plugs may be present [9].

Because of the rarity of PRP, randomized control trials evaluating the efficacy of treatment are limited. Therapeutic options have included topical and oral retinoids, corticosteroids, methotrexate, and phototherapy amongst others, however the responsiveness of PRP to therapy is generally regarded as stubborn and refractory [10]. In the limited reported cases of ponatinib-induced PRP-like eruptions, treatment has primarily been with topical corticosteroids, topical retinoids, and keratolytics, and generally has not required cessation of ponatinib [6].

With the emergence of biologics, these newer therapies have been trialed with relative success for the treatment of PRP. A recent systematic review analyzing the efficacy of various biologics found that biologics resulted in a statistically significant higher response rate compared to oral retinoids [11]. Additionally, a therapeutic response was noted in 4.6 weeks on average with biologic therapy, compared to 8.1 weeks with oral retinoids [11]. Furthermore, the authors found that secukinumab and ustekinumab had the highest response rates of the included biologics, although it should be noted that sample size was limited [11]. In other case series, ustekinumab showed a marked to complete response in 78% of patients [10]. Further, longitudinal observation has shown that biologics can result in long term disease control and remission [12].

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CHICAGO DERMATOLOGICAL SOCIETY **Case #3**

PRESENTERS

Gaurav Agnihotri, MD, Christopher R. Shea, MD, Amy Xu, MD

Patient A

HISTORY OF PRESENT ILLNESS

A 36-year-old female presented for evaluation of her left great toenail. Symptoms began several weeks prior to evaluation at the left proximal nail fold, with tenderness,

swelling, and redness after use of tight-fitting shoes and accidental trauma. Acute paronychia or joint injury was initially suspected. Needle aspiration of the paronychia was attempted with no remarkable drainage. The patient was prescribed empirical treatment of cephalexin 500mg twice daily for 14 days.

At one month follow up, the patient reported that the pain persisted, and similar changes of redness and tenderness had begun on the proximal nail fold of the right great toenail after traumatizing that toe as well. Of note, she also reported that both great toenails had become yellowish in color and "stopped growing." At this visit the patient was prescribed ketoconazole 2% cream and clobetasol 0.05% cream and instructed to mix both and apply to the left great toe twice daily for 2 weeks. X-ray of the left foot demonstrated no fractures.

REVIEW OF SYSTEMS

Negative for fevers/chills, headaches, joint pain.

PAST MEDICAL HISTORY

Hypothyroidism

MEDICATIONS

Levothyroxine

ALLERGIES

Penicillin

FAMILY HISTORY

No pertinent history

PHYSICAL EXAM

Upon initial evaluation, the proximal nailfold of the left great toe demonstrated an erythematous and edematous non-fluctuant plaque. There were no limitations in the range of motion of the distal interphalangeal joint or tenderness with movement. The nail plate of the right and left toenail appeared yellowed and brittle, but no thickening or significant discoloration was noted. Subsequent examinations showed similar, but milder, changes of the right great toe, with interval development of some hemorrhagic crusting at the left proximal nail fold. The other toes remained clear.

LABORATORY AND IMAGING DATA

2 view X-rays of the left foot showed focal soft tissue swelling dorsal to the interphalangeal joint of the great toe, but no underlying fracture or dislocation. The joint itself and the remainder of the foot were unremarkable.

HISTOPATHOLOGY

N/A

DIAGNOSIS

Retronychia

TREATMENT AND COURSE

The patient underwent complete nail plate avulsion of the left and right great toenails. A portion of the left great toe proximal nail fold was biopsied with a #15 blade and sent for histologic analysis, which showed granulation tissue. The nail plate was negative for fungus on GMS staining. At 4 month follow up, the patient noted slow regrowth of the bilateral great toenails, with normal appearing nail plate and no further pain.

DISCUSSION

Retronychia

Retronychia was initially described in 1999 and recognized as a distinct clinical entity in

2008 [1,2]. Retronychia represents proximal nail plate ingrowth posteriorly into the nail fold, resulting in inflammation, arrested nail growth, unresolving paronychia with granulation tissue underneath the proximal nail fold, thickening of the proximal nail fold, and xanthonychia (yellowish nail plate discoloration) [3,4]. The diagnosis is made clinically. Most case reports have been in young adult females, predominantly affecting the great toenails.

Trauma has been identified as the initial step in the development of retronychia. Trauma pushes the nail backwards and upwards, causing a split of the nail plate from the matrix between the basal compartment and keratogenous zone, impeding longitudinal nail growth [3,5]. It is suspected that the old nail plate adheres firmly to the distal nail bed so when the matrix makes a new underlying plate, it is unable to push the old plate out, causing a stacking of nail plates [2]. Alternatively, some have suggested that severe distal onycholysis secondary to trauma can also precipitate retronychia [4]. Distal onycholysis allows for the back-and-forth movement of the nail plate, and eventually the proximal end of the nail plate penetrates the nail fold, resulting in granulation tissue formation, which exudes from under the nail fold spontaneously or under minimal pressure. Due to the repeated backward movements, it may appear that the nail is not growing [5].

Surgical nail plate avulsion is the gold standard of treatment for retronychia, particularly in later stages evidenced by intense paronychia or proximal nail plate elevation [6]. Recurrence of retronychia is possible after avulsion but very uncommon [6]. Conservative measures may be helpful in early stages such as topical or intralesional corticosteroids and taping [6].

Patient B

HISTORY OF PRESENT ILLNESS

A 50-year-old male with a history of alcoholic cirrhosis status post liver transplant about 3 months prior to presentation presented for abnormal appearing nails on both hands for the past month. He noted discoloration of his nail that was dark pink in color. He denied trauma to the nails. Nails were asymptomatic.

REVIEW OF SYSTEMS

No fevers, chills, night sweats, easy bruising, joint pain

PAST MEDICAL HISTORY

Alcoholic cirrhosis of liver, asthma, acute kidney injury

MEDICATIONS

Aspirin, magnesium oxide, oral tacrolimus

ALLERGIES

NKDA

SOCIAL HISTORY

Works in insurance
Used to drink alcohol. Denies tobacco use.

FAMILY HISTORY

None pertinent

PHYSICAL EXAM

All right sided fingernails and the left third to fifth fingernails with bright red vascular appearing crescent noted over the proximal lunulae and visible through the cuticle. Few horizontal ridges (Beau's lines) were noted at the distal edge of the red lunulae.

LABORATORY AND IMAGING DATA

None pertinent

HISTOPATHOLOGY

None pertinent

DIAGNOSIS

Red Lunulae

TREATMENT AND COURSE

The patient's red lunulae were thought to be secondary to his recent liver transplant. He was advised that the nail changes would likely grow out with time. The patient was also advised to avoid trauma or manipulation of the nails. At follow up visit 4 months later, the discoloration had grown out with residual distal nail dystrophy. The proximal nail fold appeared normal though with mild opaqueness to the nail plate.

DISCUSSION

Red lunulae

Red lunula was initially described in 1954 in patients with cardiovascular disease and alopecia areata [7,8]. As the name aptly describes, 'red lunula' is erythema that substitutes the normally white lunula; occasionally there may be a peripheral white band distal to the red lunula. It most commonly affects the thumbs where the lunulae are most commonly visible but has been reported to affect all fingernails and toenails [9]. The erythema blanches when the nail plate is pressed.

Red lunulae have been associated with various dermatologic entities such as alopecia areata, vitiligo, lichen sclerosus et atrophicus, psoriasis, and twenty nail dystrophy [9]. It has also been associated with connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and Sjogren's syndrome [9]. Heart and hematopoietic stem cell transplant have also been associated with red lunulae [10,11]. Various other endocrine, gastrointestinal, infectious, hematologic, neoplastic, and pulmonary diseases have been associated with red lunulae; the significance of the associations is yet to be determined.

The first histopathologic examination of a red lunula in a patient with chronic obstructive pulmonary disease, diabetes, and cirrhosis was reported in 1989 [12]. The biopsy did not reveal any abnormalities. In 2013, another biopsy of a red lunula in a patient with erythrocytosis demonstrated increased vascularity in the papillary dermis of the distal nail matrix [13]. The etiology of red lunulae remains unknown. Several theories include increased arterial blood flow, a proliferation of capillaries, or increased vasodilation [7,13]. The duration of red lunulae is variable; there have been reports of red lunulae persisting for years, while some faded over weeks [14,15].

We present these cases to highlight two uncommon yet distinctive nail conditions and their associated evaluation and management.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #4**

PRESENTERS

Brooke Cui, MD, Arlene Ruiz De Luzuriaga, MD, MPH, MBA, Keyoumars Soltani, MD; Sarah Stein, MD

HISTORY OF PRESENT ILLNESS

A 13-year-old female with agenesis of the corpus callosum, seizure disorder, severe developmental delay who is nonverbal, non-ambulatory and G-tube dependent presented as a new patient to the dermatology clinic with a 2-week history of a worsening blistering eruption not responsive to multiple courses of antibiotics.

PAST MEDICAL HISTORY

Agenesis of the corpus callosum, epilepsy, severe developmental delay, neuromuscular scoliosis, non-ambulatory, G-tube dependent
Last received vaccines at 2 years old (no recent COVID or flu vaccines)

FAMILY HISTORY

No history of blistering disorders

SOCIAL HISTORY

Lives at home with mother who provides full-time care

MEDICATIONS

Levetiracetam (Keppra) 750mg BID
- Has been on brand-name version x 10 years, no recent changes

Cannabidiol (Epidiolex) 5.8mg BID (100mg/ml oral solution)
- Taken for 8 years, no recent changes

Levocarnitine (Carnitor) 330mg BID

Rick Simpson oil (RSO)/Tetrahydrocannabinol (THC) oil
- Taken for years with no recent changes

No other OTC medications (including NSAIDs)

ALLERGIES

Penicillin, increased seizure activity

Dextrose, on ketogenic diet

PHYSICAL EXAMINATION

Perioral cheeks, nasal tip, chin and upper chest with scattered eroded and crusted plaques with underlying erythema. External lips moderately dry with scaling and few fissures; oral mucosa intact without evidence of bullae, vesicles or erosions.

Extremities, including the palms and soles, with numerous tense bullae and erosions, some bullae arising from pink patches and thin edematous arcuate to annular plaques; some bullae filled with hemorrhagic fluid, most bullae containing clear serous fluid.

NOTABLE LABORATORY RESULTS

Laboratory Study	Patient Result	Reference Range
ELISA BP 180	117 RU/mL	< 20 RU/mL
ELISA BP 230	68 RU/mL	< 20 RU/mL

CBC with differential: within normal limits; no elevation of eosinophils

IMAGING

None

DERMATOPATHOLOGY

Punch biopsy from the right forearm, H&E stain - subepidermal bulla with eosinophils and neutrophils with superficial perivascular lymphocytic and eosinophilic inflammatory infiltrate.

Direct immunofluorescence - linear IgG and C3 at the epidermal basement membrane zone junction and around adnexal structures.

DIAGNOSIS

Bullous Pemphigoid

TREATMENT & COURSE

Treatment was initiated with prednisone 1 mg/kg/day and fluocinonide ointment. The impetiginized lesions were treated with mupirocin 2% ointment and a 10-day course of oral clindamycin. The larger bullae on the hands were drained in the office at the initial visit. The patient's mother was instructed on how to sterilely drain future large tense blisters and necessary supplies were provided. Fluocinonide ointment was tapered to triamcinolone ointment after 2 weeks.

At the follow up visit 3 weeks later, all blisters were healing with residual erythematous patches and there were no signs of ongoing blister formation. Dapsone was started at 1mg/kg/day (this dose was

selected due to potential dose elevation with concomitant cannabidiol administration). The prednisone dose was tapered slowly over about 12 weeks. Triamcinolone ointment was continued for use on any emerging erythematous patches or plaques. There has been no recurrence of blistering to date.

DISCUSSION

Bullous pemphigoid (BP) is an autoimmune bullous disorder (AIBD) causing subepidermal blister formation. It presents primarily in patients older than 60 years (mean age 75 to 81 years old) [6]. It is rare in children, occurring more frequently in early childhood, and is even more rare in adolescents (with only 14 published cases) [1-3]. Bullous pemphigoid is a chronic condition in adults with significant morbidity, and mortality of 10-40% in the first year [6]. The condition has a much more favorable course in children with most achieving durable remission and fewer hospitalizations compared to children with pemphigus or other AIBD [3].

Bullous pemphigoid is caused by IgG autoantibodies to the hemidesmosomal plaque. The binding of these antibodies causes complement activation and degeneration of the extracellular matrix proteins resulting in subepidermal blistering. The most common target antigens are BP180 (also known as BPAg2 and type XVII collagen) and BP230 (also known as BPAg1)[6]. Triggers for the formation of these autoantibodies are thought to be medications, vaccines, infections, transplants or physical factors (such as trauma, surgery, thermal/electrical burns, ultraviolet exposure, radiotherapy, and possibly photodynamic therapy) [4].

Drug-induced bullous pemphigoid more commonly affects younger age groups. Over 50 different medications have been associated with the development of bullous pemphigoid. Medications identified as triggers have included antibiotics, nonsteroidal anti-inflammatories, salicylates and others, including levetiracetam which is pertinent in our case. Two published case reports of levetiracetam-induced BP describe disease onset within 2-3 months of starting the medication, while our patient had been on the medication for 10 years. Extensive literature search was unable to identify any reports of cannabidiol or other cannabis-related agents associated with the development of bullous pemphigoid [7,8].

Clinical features of BP are similar in child and adult presentations, though disease distribution is somewhat different. A non-bullous (early) phase presents with pruritus and fixed urticarial papules/plaques (often annular). Subsequently the bullous phase presents with tense, fluid-filled vesicles/bullae arising on an urticarial background. In adults, the typical distribution includes the trunk, flexural extremities and intertriginous areas [6]. Mucosal lesions are relatively common in children, occurring in about 14.8% of infant cases and 55% of early adolescent cases, while somewhat less typical of adult cases (10-30%) [2,3]. Palm and sole involvement is reported most commonly in infants (those < 1yo); interestingly this finding was also present in our patient and is not characteristic of adult BP[1,3].

Histology is comparable in children and adult BP cases [1,3]. Histology in the urticarial phase demonstrates eosinophilic spongiosis with vacuolization of the dermal/epidermal junction (DEJ) as well as eosinophils lining up along the DEJ and scattered in the superficial dermis. The bullous phase demonstrates a subepidermal split with numerous eosinophils in the blister cavity and dense dermal lymphocytic and eosinophilic inflammation [6].

Direct immunofluorescence (DIF) studies from peri-lesional (intact) sites are very sensitive, demonstrating linear IgG and C3 deposition located along the DEJ in an n-serrated pattern. DIF performed on salt-split skin demonstrates binding of antigens to the roof of the blister. Indirect immunofluorescence is 60-80% sensitive when performed on salt-split normal human skin. ELISA is 80-90% sensitive with titer levels that correlate with disease activity and are useful for monitoring the response to treatment [6]. Interestingly, BP180 ELISA levels seem to be significantly higher in infants (and was noted in our patient's case) [3].

The first line treatment for bullous pemphigoid is systemic steroids 1-2mg/kg/day in combination with a steroid sparing immunosuppressive agent. Alternatively, studies have shown that the use of super-potent topical steroids can be effective, even with large areas of involvement. However there is an inherent risk of systemic absorption in young children with a higher surface area to body mass ratio. Other treatment options include tetracyclines in combination with nicotinamide for mild disease; dapsone has been used in mucosal-predominant BP; and rituximab, intravenous immunoglobulin and plasma exchange for refractory disease [6].

A case series in Pediatric Dermatology in 2019 identified 9 early adolescent cases (10-13 year olds) of bullous pemphigoid and 5 cases occurring in middle adolescence (14-17 year olds). Focusing on the early adolescence subgroup, the group in which our patient falls, mucosal surfaces were affected in 5 of the 9 cases (but none of the middle adolescent cases). Treatments entailed systemic steroids in combination with a steroid sparing agent, including dapsone, azathioprine or erythromycin/nicotinamide. Relapses were reported in 3 of the 9 early adolescent cases with recurrence ranging from 1 month to 2 years after initial disease control [2].

In light of our patient's complex neurological comorbidities, we reviewed the literature on BP associated with neurological disorders. A retrospective study in the Journal of the European Academy of Dermatology and Venerology from a single center in Germany looked at the association between BP and neurological disorders in 183 adult patients. These authors found a statistically significant association between BP and dementia, Parkinson's disease and stroke, theorizing that the association between BP and these neurological disorders may be due to cross reaction of BP autoantibodies or their isoforms with antigens expressed in the brain and neuronal tissue. However, the immunological mechanisms have not been fully elucidated [9].

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CHICAGO DERMATOLOGICAL SOCIETY **Case #5**

PRESENTERS

Cody Funkhouser, MD, Arlene Ruiz de Luzuriaga, MD, MPH, MBA, Keyoumars Soltani, MD, Angad Chadha, MD

HISTORY OF PRESENT ILLNESS

A 69-year-old female was transferred from a community hospital to the University of Chicago Medical Center Burn Unit due to concern for Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). She had initially presented to the outside hospital from a nursing home with a two-day history of an erythematous rash that started on her posterior neck and spread diffusely to her entire body. She noted a prodrome of fatigue and malaise but denied any fevers, arthralgias, or myalgias. She had been treated with dexamethasone for COVID-19 four weeks prior to presenting. She denied any other new medications.

PAST MEDICAL HISTORY

Renal cell carcinoma treated with nephrectomy (2003), multiple sclerosis complicated by blindness, dementia, hypertension, coronary artery disease, COVID pneumonia (3 months prior)

MEDICATIONS

Unknown multiple sclerosis infusion medication, rosuvastatin, ezetimibe, lisinopril, ibuprofen

FAMILY HISTORY

Noncontributory

PHYSICAL EXAM

Diffuse erythema with widespread desquamation and focal areas of superficial erosion, accentuated in intertriginous areas. Negative Nikolsky sign. Perioral region had multiple papules and plaques with honey colored crusting. Mucosal lips, oropharynx, nasal area, conjunctiva largely clear. Palms and soles were clear.

LABORATORY DATA

White blood cell: 18.6 $x10^3$/µl (3.5-11)
Platelets: 78 $x10^3$µl (150 – 450)
Sodium 126 mmol/L (135-145)
Creatinine 0.44mg/dL (0.5-1.4)
Bacterial culture, groin: Methicillin resistant *Staphylococcus aureus*, clindamycin resistant
Bacterial culture, perioral: Methicillin resistant *Staphylococcus aureus*, clindamycin resistant

DERMATOPATHOLOGY

Histopathological analysis of a punch biopsy specimen from the right arm showed parakeratosis, neutrophilic serum crusting, and intracorneal and subcorneal acantholysis with minimal inflammation. There was psoriasiform hyperplasia with pallor in the upper half of the epidermis and prominent focal papillary dermal edema with extravasated erythrocytes. There was a superficial perivascular lymphohistiocytic infiltrate. The methenamine silver stain was negative for fungi and the Gram stain was negative for bacteria.

Direct immunofluorescence was also performed and was non-specific. It demonstrated large amounts of IgG and fibrinogen throughout the dermis, some areas of immunoglobulin deposition, fibrinogen in the stratum corneum (crust), and large numbers of inflammatory cell infiltrates in the upper and mid dermis.

DIAGNOSIS

Staphylococcal scalded skin syndrome

TREATMENT AND COURSE

The patient was initially admitted to a community hospital from a nursing home due to a progressive diffuse erythematous rash with associated desquamation and bullae. She was treated with IV acyclovir due to concern for disseminated herpes zoster, as well as linezolid and piperacillin/tazobactam. Herpes simplex virus 1 + 2 PCR and varicella PCR were negative. Given clinical deterioration, she was transferred to the University of Chicago Medical Center.

Examination showed diffuse erythema with widespread desquamation and focal areas of superficial erosion. The perioral region had multiple honey colored crusted papules and plaques but no clear mucositis. Nikolsky sign was negative. Punch biopsies for H&E and direct immunofluorescence were obtained. Bacterial cultures from the perioral and groin regions were positive for methicillin resistant *Staphylococcus aureus*, which was also clindamycin resistant. Based on the clinical presentation, histology, and culture data, a diagnosis of Staphylococcal

scalded skin syndrome was made. The patient was started on vancomycin with improvement in her eruption. She was transitioned to linezolid on discharge and completed a fourteen day course.

DISCUSSION

Staphylococcal scalded skin syndrome (SSSS) is a rare toxin-mediated skin infection [1]. SSSS occurs as a result of toxigenic strains of *Staphylococcus aureus* which produce exfoliative toxins A & B. The toxins cause hydrolysis of the amino-terminal of the extracellular domain of desmoglein 1, subsequently resulting in disruption of keratinocyte adhesion in the stratum granulosum and eventual bullae formation [1,2]. SSSS often starts with a localized *S. aureus* infection, although clinically this infection may not be apparent. Commonly, the primary source of infection in adults is the upper respiratory tract, pneumonia, or bacteremia, while in neonates it is the umbilical area or diaper area [3]. Exfoliative toxins A + B are then disseminated hematogenously and produce epidermal damage at distant sites [3].

After initial infection there is an incubation period of 1 to 10 days; during this time, patients may have a prodrome of fever and malaise [1]. SSSS then evolves with abrupt onset of faint erythematous tender patches that often begin on the face and intertriginous areas. The rash then coalesces into confluent scarlatiniform erythema. Flaccid bullae can develop which then lead to large areas of superficial epidermal detachment. Nikolsky sign is typically positive [3]. Desquamation continues for one week and then heals without scarring [3]. SSSS typically does not involve the mucous membranes, as desmoglein 1 is found in the upper epidermis but not on mucosal membranes. Desmoglein 3 is present in the lower epidermis and mucosal membranes and is able to compensate for lysis of desmoglein 1; the presence of desmoglein 3 maintains adhesion in mucous membranes and lower epidermis [1,3].

The diagnosis of SSSS is mainly clinical and can be confirmed by culturing *S. aureus* from a suspected primary infection [4]. Culturing bullae is not useful as the bullae are formed as a result of the circulating exfoliative toxins and *S. aureus* is not present in skin lesions [4]. Histologically, SSSS demonstrates subcorneal cleavage which may contain acantholytic cells [1,2,4]. Cellular necrosis and inflammatory cell infiltrate are typically absent [1].

The differential for SSSS includes SJS, TEN, bullous impetigo, toxic shock syndrome, and epidermolysis bullosa [4]. SSSS can be differentiated from SJS and TEN, as they are typically linked to a medication and have full thickness epidermal necrosis and vacuolar changes on histology [1]. SSSS can be differentiated from bullous impetigo as bullous impetigo is typically seen in newborns and infants, has sharply demarcated bullae without surrounding erythema, occurs at the primary site of infection, Nikolsky sign is negative, and *S. aureus* can be cultured from the skin lesions [1].

Treatment of SSSS consists of systemic antibiotics that cover *S. aureus*. Topical antibiotics are not effective. Supportive care focusing on management of fluid status, nutrition and temperature regulation should be emphasized. These patients are also at high risk of secondary bacterial skin infections; antibiotics should be broadened if this concern arises [4].

Although this case illustrated SSSS in an adult, SSSS is more common in young children, with an annual prevalence of 7.67 cases per million in children versus 0.98 cases per million in adults [1,5]. Two potential hypotheses for a higher incidence of SSSS in children compared to adults is that children have not yet developed protective antibodies against staphylococcal toxins and that children's kidneys are not as effective in excreting the exfoliative toxin [1].

Children are often healthy prior to developing SSSS, while adults typically have underlying risk factors [1,6]. The main risk factors for SSSS in adults are impaired renal function and immunosuppression, including other comorbidities that impair immune response to bacterial infection such as diabetes or human immunodeficiency virus infection [1,3,6,7]. The patient discussed here had normal kidney function but did have a history of renal cell carcinoma treated

with nephrectomy. She did not have any known immunosuppression, although she was on an unknown infusion for her multiple sclerosis. In addition, blood cultures for *S. aureus* are often positive in adults and usually negative in children [3,7]. There are also mortality differences between children and adults who have SSSS, as the mortality in children is 2.6-11% compared to 40-63% in adults [3]. This difference is likely due to the underlying comorbidities more often seen in adults [3,8].

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CHICAGO DERMATOLOGICAL SOCIETY **Case #6**

PRESENTERS

Scott C. Blaszak, MD, Christopher R. Shea, MD, Angad Chadha, MD

HISTORY OF PRESENT ILLNESS

A 65-year-old female with a history of coronary artery disease status post coronary artery bypass graft surgery, aortic valve replacement with a bovine valve complicated by aortic stenosis status post recent transcatheter aortic valve replacement (TAVR) was evaluated in the hospital for progressive, tender non-healing wounds on the right lower abdomen and right inguinal crease.

The patient had a 1-month history of progressive, tender, non-healing wounds on her right lower abdomen and right inguinal crease. She noted development of exquisitely tender wounds

approximately 1-week after her TAVR procedure. Patient was treated at a community hospital with multiple antibiotic courses, valacyclovir, and oral fluconazole without significant improvement.

PAST MEDICAL HISTORY

Coronary artery disease status post coronary artery bypass graft surgery, aortic valve replacement with bovine valve complicated by aortic stenosis status post TAVR, peripheral vascular disease status post stents of left iliac artery, right superficial femoral artery and above knee amputation of the right lower extremity, chronic obstructive pulmonary disease, and hypertension.

FAMILY HISTORY

No known family history of dermatologic conditions.

MEDICATIONS

Aspirin, clopidogrel, furosemide, losartan, atorvastatin, bupropion, escitalopram oxalate, and famotidine.

REVIEW OF SYSTEMS

Pertinent negatives include lack of fevers, chills, abdominal pain, bloating, diarrhea, arthralgias, and oral/nasal ulcerations.

PHYSICAL EXAMINATION

Multiple discrete, tender circular to oval-shaped ulcerations of varying sizes from 1-4 cm with erythematous borders and firm subcutaneous nodularity of the right lower abdomen and right inguinal crease. Subsequently, during the admission, the patient developed subtle retiform purpura on the right lower abdomen.

LABORATORY AND IMAGING DATA

CBC with differential: Mild anemia with slight eosinophilia
Basic metabolic panel: [WNL]
Hepatic function panel: [WNL]

Bacterial tissue culture: Methicillin resistant Staphylococcus aureus (MRSA)
Acid fast bacilli culture & stain: Negative
Fungal tissue culture: Negative
Blood cultures x 2: Negative

DERMATOPATHOLOGY

Initial punch biopsy of the ulcer edge was non-specific and demonstrated focal ulceration with a mixed neutrophilic and lymphocytic inflammatory infiltrate.

Incisional skin biopsy of the new onset retiform purpura on the right lower abdomen demonstrated a superficial and deep lymphocytic perivascular and peri-eccrine infiltrate. Deep in the dermis there were collections of histiocytes and foreign-body giant cells, which focally engulfed a basophilic blue-gray material. Additionally, the basophilic blue-gray material was seen intravascularly in the subcutis. Observation with polarized light was negative for birefringent foreign material. Lipomembranous change was noted within the adipocytes.

Von Kossa stain was negative for calcium. Gram stain, fite stain, methenamine silver stain, and periodic acid-Schiff stains were negative for infectious etiologies.

DIAGNOSIS

Hydrophilic polymer embolization

TREATMENT AND COURSE

Initially, the patient was managed with antibiotics due to a positive bacterial tissue culture which demonstrated MRSA. However, given lack of improvement after a 7-day course of IV vancomycin an incisional biopsy was performed from a newly livedoid area which demonstrated intravascular basophilic foreign body material confirming a diagnosis of hydrophilic polymer embolization, likely from the patient's recent TAVR. The patient was started on prednisone 60 mg daily for 2 days and was decreased to 30 mg daily for 4 weeks with a subsequent plan for a prolonged taper. Ulcerated areas were managed with mupirocin ointment twice daily and covered with a non-adherent pad until healed. The patient was scheduled to return to the outpatient dermatology clinic 1-month after discharge but was unable to return to clinic. Follow up was performed via a telephone encounter and the patient reported complete resolution of previous ulcerations without interval development of new ulcerations.

DISCUSSION

Endovascular procedures are commonly used for management of blood vessel and cardiac pathology. Endovascular procedures utilize multiple different devices to access and allow instrumentation within vascular spaces, including placement of stents, sheaths, catheters, and guide wires [1]. Many devices utilize a polymer coating to help reduce friction, limit vascular spasm, and increase maneuverability [2]. However, introduction of a foreign material carries a risk of potential embolization and ischemic complications, ranging from cutaneous findings to pulmonary infarction, stroke, and potentially death [3]. Cutaneous findings may serve as a sign of embolization to other vital internal organs. Hydrophilic polymer emboli are a rare and potentially under recognized entity that needs to be considered after recent endovascular procedures.

Cutaneous clinical presentation of hydrophilic polymer emboli varies from sudden onset non-palpable purpura, livedo reticularis/racemosa, and painful non-healing ulcers or nodules [4]. In the literature, there have been few case reports of cutaneous complications after a recent endovascular procedure. Timing of cutaneous findings range from within a few hours to weeks after intravascular intervention. The majority of patients developed unilateral livedo racemosa of the lower extremity. All cases required histopathologic evaluation for diagnosis of hydrophilic polymer emboli [1,6,7].

Histologic evaluation of hydrophilic polymer emboli may demonstrate intravascular lamellated, finely granular, non-refractile, non-polarizable basophilic material. Additionally, evidence of a foreign body reaction may be present [5].

Treatment is often supportive as the polymer materials biodegrade in vivo, ranging from 2-weeks to 1-month [3]. However, corticosteroids, antiplatelet agents, and surgical resection of necrotic wounds have been utilized for a few cases [4].

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CHICAGO DERMATOLOGICAL SOCIETY **Case #7**

PRESENTERS

Maria Estela Martinez-Escala, MD, PhD, Oluwakemi Onajin, MD, Christopher R. Shea, MD, Mark D. Hoffman, MD

HISTORY OF PRESENT ILLNESS

A 50 year-old woman with questionable history of systemic lupus erythematosus (SLE) and venous dermatitis presented to Dermatology for evaluation of a 2-week history of indurated plaques on the upper arms. She also described redness and swelling of the lower extremities ongoing and

stable for the past two years. A biopsy of an arm plaque had features consistent with lupus erythematosus panniculitis (see Histopathology section). Evaluation by Rheumatology deemed the findings insufficient for SLE, and the patient was prescribed hydroxychloroquine 200 mg BID. She was diagnosed with lipodermatosclerosis of her lower extremities, which was managed with compression stockings and pentoxifylline 400 mg TID. In the following months, the nodules on the upper arms resolved with residual lipoatrophy, and the indurated erythematous plaques of the lower extremities improved with residual hyperpigmented induration on bilateral ankles. Two years after her initial presentation, she developed new tender subcutaneous nodules on the anterior lower extremities. Another skin biopsy of the lower legs was performed.

REVIEW OF SYSTEMS

Positive for joint pain of the knees. Negative for fever, weight loss, fatigue, photosensitivity, or oral aphthosis.

PAST MEDICAL HISTORY

? SLE in 2013 (positive ANA and dsDNA, low C4)
Venous dermatitis
Central centrifugal cicatricial alopecia
Seizure disorder
Chronic urticaria
Intellectual disability

MEDICATIONS

Hydroxychloroquine 200 mg twice a day
Pentoxifylline 400 mg three times a day
Lamotrigine 150 mg twice daily
Levetiracetam 750 mg daily
Lorazepam 1 mg q6h prn
Metformin 500 mg twice a day

ALLERGIES

No known allergies

FAMILY HISTORY

No family history of SLE

PHYSICAL EXAM

Bilateral shoulders and upper arms with mildly scaling brownish firm depressed plaques.

Bilateral lower legs with pitting edema and erythematous indurated plaques with overlying scale.

LABORATORY AND IMAGING DATA

Workup at the time of initial referral to rheumatology was remarkable for:

Positive ANA (1:320, homogeneous pattern)
C4 17 mg/dl (N 18-45)
ESR 60 mm/hr (N <39)
CRP 17 mg/L (N <5)

Normal, negative, or unremarkable results included: complete cell blood count (CBC), comprehensive chemical panel (CMP), rheumatoid factor (RF), anti-Smith (Sm) antibodies, anti-RNP antibodies, complement 3 (C3), urinalysis

Work up two years later was remarkable for:

ESR 53 mm/hr (N <39)

CRP 17 mg/L (N <5)

Normal, negative, or unremarkable results included: CBC, CMP, lactate dehydrogenase, RF, ds-DNA antibodies, anti-Sm antibodies, anti-RNP antibodies, C3, C4, urinalysis

Positron emission tomography/Computed tomography: diffuse hypermetabolic activity in the external iliac and inguinal lymph nodes

Ultrasound guided biopsy of right inguinal lymph node: no evidence of lymphoma

HISTOPATHOLOGY

First biopsy (at presentation) of the right upper arm: There was vacuolar interface alteration at the dermal epidermal junction, a superficial and deep dense perivascular and periadnexal dermal and subcutaneous lymphocytic infiltrate and lymphocytoclastic dust. There was also increased reticular dermal interstitial mucin deposition. There was a prominent infiltrate of small size lymphocytes involving the fat lobules, with rimming of lymphocytes identified. There was a hyaline sclerosis extending to the fat lobules.

Second biopsy (two years later) of the right lower leg: the epidermis demonstrated only focal interface vacuolization. There was a sparse perivascular lymphocytic infiltrate within the superficial to mid dermis with increased dermal mucin. There was a predominantly lymphocytic infiltrate in the subcutis within the fat lobules. The lymphocytes demonstrated atypical features with large, dark staining nuclei rimming fat lobules. These were CD3, CD8, TIA-1, granzyme B and T-cell receptor (TCR) beta. Ki-67 demonstrated an increased proliferation index in the atypical large cells rimming the adipocytes. CD123 was expressed in a few scattered cells but no clusters. CD56, Epstein-Barr encoding region in situ hybridization, and TCR delta were negative. The TCR gene rearrangement was inconclusive.

DIAGNOSIS

Subcutaneous panniculitis-like T-cell lymphoma in a patient with lupus erythematosus panniculitis

TREATMENT AND COURSE

Treatment with methotrexate 20 mg weekly plus 1 mg daily of folic acid were initiated, and three months later the patient achieved clinical remission. During the subsequent 6 months of follow-up, methotrexate was tapered to 10 mg weekly, and she remained in complete remission.

DISCUSSION

Lupus erythematosus panniculitis (LEP) is a clinical variant of chronic cutaneous lupus that may manifest in isolation or in association with discoid lupus erythematosus (DLE) or SLE. It is most often seen in females, yet it may affect both sexes. The age of presentation ranges from 30 to 60 years. It presents as single or multiple tender subcutaneous nodules most commonly located on the lateral aspects of the proximal upper extremities, shoulders, face, buttocks and scalp. It is infrequently observed in the lower extremities [1]. Overlying features of DLE (scale, follicular plugging, dyspigmentation) are seen in 28% of the cases and, when present, the term lupus profundus is preferred [2]. Classic histopathologic features of LEP include presence of hyaline fat necrosis, lymphoid aggregates and lymphoid follicle formation, and lobular panniculitis with peri-septal involvement. Other less specific findings are lymphocytic vasculitis, mucin deposition, infiltrates of plasma cells and eosinophils, as well as presence of karyorrhexis or lymphocytic nuclear dust. The lymphocytic infiltrate is usually composed of alpha/beta T-cells with slight prevalence of CD4+ over CD8+ cells. The majority of the cases show a polyclonal TCR gene rearrangement. The lupus band test is positive in 70% of the patients [1]. Drug therapy may include hydroxychloroquine, thalidomide and anecdotally mycophenolate mofetil, azathioprine or cyclosporine. The course is usually chronic and relapsing, and lesions resolve with depressed lipoatrophic areas.

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is a rare cytotoxic cutaneous T-cell lymphoma. Mean age of presentation is 46.5 years, yet it is noteworthy that 20% of the cases present in children [3,4]. Clinical presentation is characterized by erythematous tender nodules predominantly located on the lower extremities, although it may affect the trunk, upper arms and head and neck. The presence of SPTCL in association with lipodermatosclerosis changes, as was and is presumed in our case, has not to our knowledge been reported in the literature. Patients may have associated systemic symptoms such fever, fatigue or weight loss. The presence of these systemic symptoms should prompt further investigation to rule out an associated hemophagocytic lymphohistiocytosis (HLH), which can be present in 15% of the cases [3,4]. Another 20% of the cases with SPTCL can be associated with autoimmune conditions such as SLE, rheumatoid arthritis, or dermatomyositis. Histopathologically, SPTCL is characterized by a dense lobular infiltrate of atypical lymphocytes, classically in a distribution rimming the individual adipocytes. Karyorrhectic debris and macrophages can also be observed. The atypical lymphocytes are CD8+ (which defines their cytotoxic phenotype), TCR alpha/beta, and negative for CD4+, CD56+, and TCR gamma/delta. Prognosis is normally good unless associated with HLH, in which cases it is often lethal. Lymph node or systemic dissemination is infrequent. Common treatments used in SPTCL are methotrexate or cyclosporine; the latter is particularly indicated when HLH symptoms are associated. Chemotherapy and stem cell transplant are used in refractory cases [4,5].

Despite the unique findings of each entity discussed above, clinicians and pathologists may occasionally find it difficult to distinguish between them. Diagnosis of either SPTCL or LEP requires clinicopathological correlation plus additional workup that may include molecular tests, direct immunofluorescence and serologic studies (such antinuclear antibodies, double-stranded DNA, complement). There have been many efforts from several research groups to describe histopathologic, molecular and even genetic characteristics that may favor diagnosis of either LEP or SPTCL. For instance, it has been noted that the presence of clusters of CD123+ plasmacytoid dendritic cells within the lymphocytic infiltrate may favor LEP over SPTCL [6]. On the other hand, high proliferative index of the lymphocytes detected by increased expression of Ki-67 (>20% of the lymphocytic infiltrate), especially on the peri-adipocytic lymphocytes, has been associated with the diagnosis of SPTCL [7]. However, a very few LEP cases have shown a proliferative index of >20%, while some SPTCL cases have demonstrated clusters of plasmacytoid dendritic cells within their infiltrate [8]. Molecular tests such as T-cell receptor gene rearrangement by polymerase chain reaction to detect T-cell clonality have been used to differentiate SPTCL from LEP. While most of the SPTCL cases have a positive T-cell clone, a very few LEP cases may have it too [8].

In addition, case series showing overlapping features of SPTCL and LEP within the same skin biopsy have been published. These cases showed similar epidemiologic, clinical presentation and outcomes seen in both SPTCL or LEP [9,10]. Finally, a case report showing coexistence of SPTCL and LEP, as seen in our case, has also been reported in the literature [11].

Gene expression profiles of SPTCL, LEP, and overlapping cases have been investigated, demonstrating molecular signatures that are distinctive between SPTCL and LEP. However, some LEP cases showed expression affinities with SPTCL [12]. Because of the overlapping features and common genetic pathways observed in selected cases of SPTCL and LEP, some authors have hypothesized that LEP and SPTCL may occupy positions along a spectrum [13,14]. Those cases that do not fulfill criteria for LEP or SPTCL are termed atypical lymphocytic lobular panniculitis, a T-cell dyscrasia with potential risk to evolve into bona fide SPTCL.

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CHICAGO DERMATOLOGICAL SOCIETY **Case #8**

PRESENTERS

Sarah Semaan, MD, Christopher R. Shea, MD, Angad Chadha, MD

HISTORY OF PRESENT ILLNESS

A 52-year-old woman with a history of Graves' disease treated with thyroidectomy and hormone replacement therapy was referred to our dermatology clinic for evaluation of swelling and painful nodules on bilateral ankles and feet. The patient started developing swelling of her bilateral ankles two years after her thyroidectomy, after a prolonged history of untreated Graves' disease and thyroid storm. She was initially evaluated by podiatry who performed an excisional biopsy and debulking procedure to help reduce swelling; pathology from this procedure showed benign adipose tissue. She was also trialed on intralesional triamcinolone and multiple short courses of oral corticosteroids without improvement. Given interval worsening of the swelling and pain, the patient was referred to orthopedic surgery for a second opinion. A magnetic resonance imaging (MRI) scan of the bilateral lower extremities showed diffuse lobulated skin thickening with underlying extensive fat reticulation extending to the medial, lateral and posterior aspect of the ankles bilaterally, with radiographic concern for inflammatory skin disease. She was then referred to dermatology for further evaluation and management. At time of dermatology evaluation, the patient was unable to stand or ambulate for long periods of time, unable to work due to this reason, and in daily pain from her ankle swelling.

PAST MEDICAL HISTORY

Graves' disease

MEDICATIONS

Levothyroxine. Supplements include ascorbic acid (vitamin C), ferrous sulfate (iron)

FAMILY HISTORY

Noncontributory

PHYSICAL EXAM

Examination of the bilateral lower extremities revealed multi-lobular firm plaques and nodules on the lower legs and ankles with overlying hyperpigmentation, variable erythema, and minimal overlying lichenification. The plaques and nodules were tender to palpation. There was also occasional mild verrucous-to-pebbly textural changes on the bilateral dorsal feet and ankles.

LABORATORY DATA

None

DERMATOPATHOLOGY

Punch biopsy of one of the plaques revealed hyperkeratosis, papillomatosis, and hyperpigmentation of the basal layer. There was significant interstitial mucin deposition within the dermis. There was no fibrosis or increase in dermal spindle cells.

DIAGNOSIS

Nodular pretibial Myxedema

TREATMENT AND COURSE

Patient was initially started on clobetasol 0.05% cream twice daily under occlusion as well as daily compression stocking from the tips of toes to knees. After biopsy confirmation of pretibial myxedema, she was started on pentoxifylline 400mg three times daily. However, one week later, the patient reported fatigue, headaches, and possible worsening leg/hand swelling after starting pentoxifylline so this medication was stopped. The patient was also referred to ophthalmology for ocular puffiness and tearing, and was found to have mild thyroid eye disease that was manageable with over the counter artificial tears.

Given her disfiguring cutaneous disease with significant associated morbidity and loss of function, the decision was made to try treatment teprotumumab, a fully humanized monoclonal antibody

targeting insulin-like growth factor 1 (IGF-1) receptor. While FDA approved for thyroid eye disease, teprotumumab has also shown clinical benefit in disfiguring/nodular pretibial myxedema.

DISCUSSION

Pretibial myxedema, also called thyroid dermopathy, is an infrequent manifestation of autoimmune thyroiditis, particularly Graves' disease. Incidence is estimated to be between 0.5 % to 4.3%. Usually, thyrotoxicosis appears first, followed by ophthalmopathy and dermopathy later in the disease course [1]. It is most commonly seen in adults with a peak onset around 50-60 years of age and while some cases can be self-limited and mild, advanced cases may cause cosmetic issues, functional problems, significant debility, and are associated with lower quality of life [2].

Pretibial myxedema is classified into 4 forms: non-pitting edema, plaque, nodular and elephantiasic form [3]. While the lesions of pretibial myxedema occur most commonly on the pretibial surfaces, there are also numerous case reports of pretibial myxedema affecting non-canonical locations including the dorsal, ankles, and toes in an elephantiasis like presentation [4, 5]. Thyroid dermopathy can also develop within surgical scars, in response to external trauma, and after episodes of prolonged standing.

The pathogenesis of pretibial myxedema is believed to be multifactorial [6]. Antibodies directed at the TSH receptor in patients with Graves' disease are known to act directly on dermal fibroblasts and stimulate the production of glycosaminoglycans, which are the major constituents of mucin. Additionally, activated thyroid-specific T-cells release cytokines IL-1a and TGF-β, further stimulating the synthesis of glycosaminoglycans by dermal fibroblasts. Finally, trauma and injury lead to the stimulation of resident T-cells and initiation of antigen specific response which results in production of glycosaminoglycans by the fibroblasts.

First-line treatment for mild pretibial myxedema includes topical application of medium to high potency corticosteroids under occlusion for 4-12 weeks. Pentoxifylline can be used for more moderate disease; this medication has been shown to cause a dose-dependent inhibition of serum-driven fibroblast proliferation and therefore decrease glycosaminoglycan synthesis [7]. For severe pretibial myxedema, B cell and antibody depletion with rituximab and plasmapheresis were found to be helpful in severely affected patients [8]. Immunomodulatory therapy with intravenous immune globulin has also been used and shown to have benefit. Surgical excision of nodules and skin grafting are not recommended because of the possibility of exuberant recurrence of localized myxedema at the site of the surgical scar.

More recently, the insulin-like growth factor 1 receptor inhibitor, teprotumumab, has also been used with impressive results and reversal of nodular or elephantiasic pretibial myxedema [9]. Antibodies directed at the TSH receptor are believed to interact with insulin-like growth factor 1 receptors and this interaction has been implicated in the glycosaminoglycan production and accumulation that results in thyroid eye disease and thyroid dermopathy. Therefore, blocking this interaction carries treatment implications in thyroid eye disease and thyroid dermopathy.

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Umar Sheikh, MD, Christopher R. Shea, MD, Angad Chadha, MD

HISTORY OF PRESENT ILLNESS

A 53-year-old female presented to the University of Chicago Dermatology Clinic for a second opinion of a widespread rash. The patient described this rash as red raised bumps that turn into brown flat spots. It had been ongoing since her late 20's. The patient reported that the rash initially started on the chest and spread to involve the popliteal fossae and then the back, arms and entire body. Her face was spared. The patient denied any oral lesions. Over the past few years she had noted nail changes with ridging but wears nail polish often. She noted that her rash did flare with stress and sweating; she felt that sun exposure helped the rash. The patient noted that she has not had a severe flare in five years. The rash was not significantly pruritic or bothersome.

The patient had three biopsies prior to presenting to our clinic. Her rash was managed for many years as Grover's disease as her most recent biopsy from her lower back with her previous dermatologist showed acantholytic dyskeratosis. Previous treatments included acitretin (duration and dose unknown) and triamcinolone cream, both with some improvement but flaring upon cessation.

PAST MEDICAL HISTORY

Hyperlipidemia

FAMILY HISTORY

Family history of premature coronary artery disease and cardiovascular disease. The patient's father passed away at age 46 from myocardial infarction and had quadruple bypass surgery in his 30's. The patient's brother has a similar rash that started in his late 30's and also has a history of four stents placed in his mid-40's. The patient's paternal grandfather had a similar rash that was never diagnosed or treated.

SOCIAL HISTORY

Lives at home with husband and daughter

MEDICATIONS

Atorvastatin

ALLERGIES

Sulfa (Sulfonamide antibiotics)

PHYSICAL EXAMINATION

The chest, back, arms, and legs had innumerable tan to light brown macules, some in reticulate configurations. The lesions were most concentrated in the popliteal fossae and upper back with a few scattered hyperpigmented macules in the axillae; on the legs and back there were several scattered erythematous papules. The oral cavity was clear. Face was spared of any lesions. Examination of the fingernails and toenails was limited due to polish in place but some evidence of longitudinal ridging and minimal distal onycholysis.

LABORATORY RESULTS

Not applicable

IMAGING

Not applicable

DERMATOPATHOLOGY

Review of outside slides revealed compact hyperkeratosis with areas of focal acantholysis within the epidermis. Elongated, finger-like strands of keratinocytes extended downwards into the dermis.

DIAGNOSIS

Galli-Galli disease

TREATMENT & COURSE

The patient's rash had features most consistent with Galli-Galli disease as the patient presented with an over 30 year history of erythematous papules that progressed to hyperpigmented macules, some with reticular configuration. Family history of a similar rash in brother and paternal grandmother also supported this diagnosis. Outside slides were re-reviewed and confirmed focal epidermal acantholysis, findings consistent with Galli-Galli disease. The patient did not have perioral scarring.

The patient was offered acitretin, phototherapy, or low dose doxycycline 20mg twice a day as potential treatment options. The patient opted for doxycycline, however she never started the medication. At her follow up appointment 6 months later, the patient noted that her rash was stable and not significantly pruritic and did not bother her. The patient thus decided to hold off any further treatment.

DISCUSSION

Galli-Galli disease was originally reported and named in 1982 by Bardach et al. after two brothers who had the disease [1]. Galli-Galli disease is characterized by erythematous macules and papules coalescing into patches and plaques with reticulate hyperpigmentation involving flexural areas. An autosomal dominant mutation in the KRT5 gene is the most common mutation identified in patients who have Galli-Galli disease or Dowling-Degos disease. Galli-Galli disease can also be associated with autosomal dominant mutations in POGLUT1, and POFUT1 genes [2]. There are atypical variants of Galli-Galli disease where brown macules may be symmetrically distributed on the trunk, lower limbs and extremities without reticular hyperpigmentation of the flexures [3].

Galli-Galli disease is a rare genodermatosis and review of reported cases notes that the age of onset can vary between 13 and 63 years with a mean age of onset around 37 years. There is no racial or gender predilection observed. Most reported cases have typical reticulated hyperpigmentation of the flexures consistent with a traditional description of Galli-Galli disease, while a minority of cases have a disseminated variant, not involving the flexural areas [3].

Galli-Galli disease is differentiated from other reticulated pigmentary disorders of the skin including Dowling-Degos disease, Kitamura disease, Haber syndrome, and reticulate acropigmentation of Dohi through clinical and histopathological differences. Galli-Galli disease and Dowling-Degos disease can be clinically identical, but suprabasal acantholysis is considered to be a unique feature of Galli-Galli disease. Histopathologic analysis will show features of the downward filiform proliferation of digitate rete ridges with basal hyperpigmentation, dermal melanosis along rete ridges, and multiple foci of acantholysis within the suprabasal and upper spinous layers [3]. Increased melanin pigmentation usually restricted to the tips of the rete ridges can be seen with Fontana-Masson staining. Hyperkeratosis and dyskeratosis have also been noted, and infiltrates can consist of lymphocytes, histiocytes and eosinophils. Dowling-Degos disease will present identically under histopathology apart from the feature of acantholysis [3]. Acantholysis is a sine qua non condition to diagnose Galli-Galli disease, while dyskeratosis is not an essential finding. The presence of dyskeratosis does not exclude the diagnosis [4].

Treating Galli-Galli disease can be difficult and most published cases report either incomplete or temporary responses to therapy. There are reports of variably successful treatment with acitretin therapy and with lasers [4]. Rundle et al. reports a case of Galli-Galli disease treated with acitretin with significantly improved skin findings and pruritus. Voth et al. reports a case of Galli-Galli disease with sustained resolution of symptoms after two treatments with erbium: Yttrium-Aluminum Garnet (YAG) laser [5]. Other therapies that have been trialed with varying degrees of success include

topical retinoids, ultraviolet B phototherapy, isotretinoin, topical and oral corticosteroids and antihistamines [4].

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CHICAGO DERMATOLOGICAL SOCIETY **Case #10**

PRESENTERS

Ekene Ezenwa, MD, Lawrence Levine, MD, Oluwakemi Onajin, MD, Keyoumars Soltani, MD

HISTORY OF PRESENT ILLNESS

A 79-year-old female presented to the University of Chicago dermatology clinic for progressive lesions on the lip and oral mucosa. The lesions had been ongoing for 7 years, but progressively worsened 2 years prior to initial evaluation. She had been seen by multiple disciplinary teams (dermatology, otolaryngology, oral surgery) and multiple biopsies were performed with various diagnoses including verruciform xanthoma, epidermal hyperplasia with ongoing inflammation, lichenoid mucositis, and squamous mucosa with ulceration and fungal infection. The lesions became progressively painful and debilitating, leading to a 50-pound weight loss given anorexia. During this time, she had been treated with topical and oral therapies, with moderate response with oral voriconazole. She had no other mucosal or cutaneous findings. She endorsed travel history to the Philippines within the two years prior to initial examination.

PAST MEDICAL HISTORY

Sjogren's Syndrome (SSA/SSB+), Rheumatoid Arthritis, Cerebrovascular Accident (2014), COVID-19 infection. HPV-status unknown.

FAMILY HISTORY

No family history of autoimmune conditions or recurrent infections

SOCIAL HISTORY

Travel to the Philippines frequently, no history of use of betel nuts
No smoking, vaping, illicit drug, or alcohol use

MEDICATIONS

Amlodipine, gemfibrozil, hydroxychloroquine, tramadol, voriconazole

ALLERGIES

No known drug allergies

PHYSICAL EXAMINATION

Her lower and left upper lip had numerous papillomatous, verrucous, exophytic, friable papules and nodular plaques. The left buccal mucosa had few scattered thin whitish plaques.

LABORATORY RESULTS

Comprehensive metabolic panel and the rest of her complete blood count were grossly unremarkable, with mildly elevated glucose. Initial tissue cultures grew few staphylococcus aureus, streptococcus agalactiae, and pseudomonas aeruginosa.

DERMATOPATHOLOGY

Initial histopathologic analysis of punch biopsy specimen from the lower lip showed hyperkeratosis, acanthosis, and focal parakeratosis. There were numerous neutrophils and bacteria in the stratum corneum, and prominent neutrophils within the epidermis. In the papillary dermis there are numerous foamy histiocytes and dilated vessels, consistent with verrucous xanthoma.

At her follow-up visit two months later, a repeat biopsy of the inner mucosa was performed. Histopathology was notable for marked papillomatosis and downward growth of large well-differentiated squamous epithelium into the underlying dermis. The squamous islands were surrounded by a dense inflammatory cell infiltrate. There was irregular crowding of keratinocytes with atypical nuclei and mitoses confined to the basal and suprabasal cell layers. Immunohistochemical staining for CK5/6 markers highlight the atypical squamous epithelial cells. Ki67 and P53 markers demonstrated increased staining in the basal and suprabasal layer of the atypical squamous epithelium

The periodic acid-Schiff stain was negative for fungi or significant basement membrane thickening. The Gram stain was negative for bacteria.

DIAGNOSIS

Verrucous Carcinoma of the Oral Cavity

TREATMENT & COURSE

After repeat biopsy was performed, the patient was referred to otolaryngology. Given the extent of her lesions and concern for cosmetic disfiguration, mapping of oral cavity biopsies was performed. However, the scouting biopsies performed by otolaryngology and interpreted by surgical pathology were diagnosed as squamous mucosa with epithelial proliferation and extensive stromal lymphoplasmacytic inflammation, with concern for an infectious component. She was subsequently referred to infectious disease. Multiple serologies (HIV, syphilis, histoplasmosis, blastomycosis, coccidiosis), cultures (AFB, bacterial), and PCR (mycobacterial, fungi, and leishmania) were performed. Additionally, the patient was also started on oral cephalexin for one month by infectious disease. She continued to follow with otolaryngology. Given her worsening pain and anorexia, debulking was performed with repeat biopsy. Repeat biopsies were consistent with verrucous carcinoma. After multidisciplinary discussion, immunotherapy was initiated as monotherapy, as resection would be highly morbid and radiotherapy likely associated with substantial toxicity. Patient was initiated on cemiplimab q3 weeks with overall improvement.

DISCUSSION

Verrucous carcinoma, previously known as Ackermann's tumor, is a rare well-differentiated variant of squamous cell carcinoma. It has an elderly male predominance, most often presenting as large exophytic tumors with verrucous or papillomatous epidermal changes [1,2]. It has a predilection for the plantar foot, genitals, and the oral mucosa. The most common sites of oral verrucous carcinoma (OVC) are the buccal mucosa, then the mandibular alveolar crest, gingiva, and tongue [3].

The etiology of OVC is not well-understood; similarly to other oral squamous cell carcinomas, it is frequently associated with smoking or tobacco chewing. HPV is a suspected factor, with up to 40% of cases with HPV strains 16 or 18 [3,4]. Additionally, the chewing of betel quid (a combination of tobacco, betel nut, and spices) has been shown to increase risk of verrucous carcinoma in Asian populations. Lastly, OVC may occur because of deterioration of premalignant lesions, including oral verrucous hyperplasia, oral lichenoid, oral submucous fibrosis, and odontogenic keratocysts [3].

Oral verrucous carcinoma can gradually penetrate the underlying tissues, leading to the destruction of the subcutis, fascia, and bone [1]. Although its slow growth contributes to a long medical history, the local aggression rarely leads to regional or distant metastasis. Therefore, oral verrucous carcinoma has a relatively good prognosis.

The differential diagnosis for verrucous carcinoma includes oral verrucous hyperplasia, oral squamous papilloma, and oral hybrid verrucous carcinoma. Verrucous carcinoma and verrucous hyperplasia share several histopathologic features, which can further impede diagnosis. Recognizing the exophytic growth pattern of verrucous hyperplasia compared to the endophytic growth pattern of verrucous carcinoma can aid in eliciting a diagnosis. Additionally, features of parakeratosis (compared to orthokeratosis predominance in verrucous hyperplasia), blunt rete pegs (compared to narrow), and frank downward growth of epithelial processes extending into the basement membrane are more common in OVC. The role of immunohistochemical staining continues to be elucidated, including Ki-67, p53, and cytoskeleton markers [5,6]. However, differentiating the two diseases may be unwarranted, as some have recommended treating verrucous hyperplasia as verrucous carcinoma given the likelihood of progression [3]. Multiple

biopsies from different sites, including involvement of the tumor margin, are recommended to differentiate the two entities and reduce treatment delay [6].

There is no gold-standard for treatment in patients with OVC. Traditionally, patients with verrucous carcinoma have been treated with surgery. Radiotherapy can be used as mono- or adjuvant therapy. However, the recurrence rates in both treatment modalities is high, ranging from 6.12 – 40% [2,3]. The role of immunotherapy, particularly PD-1/PDL-1 inhibitors, continues to be elucidated, with our patient experiencing substantial response after ten months of cemiplimab every three weeks. Cemiplimab acts as a recombinant IgG4 human monoclonal antibody PD-1 inhibitor, theoretically producing an anti-tumor response. It is the first FDA-approved immunotherapy treatment for locally advanced cutaneous squamous cell carcinoma in patients who are not candidates for surgical or radiotherapy, with a positive safety and efficacy profile [7].

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