P H I L A D E L P H I A D E R M A T O L O G I C A L

S O C I E T Y M E E T I N G

April 16, 2021

THE CHILDREN'S HOSPITAL OF PHILADELPHIA

PHILADELPHIA, PENNSYLVANIA 19104

THE PHILADELPHIA DERMATOLOGICAL SOCIETY

THE CHILDREN'S HOSPITAL OF PHILADELPHIA

April 16, 2021

AGENDA

3:30 PM – 4:00 PM	Preview of Clinical Photographs
4:00 PM – 5:45 PM	Scientific Discussion presented by Dr. James Treat

The American Academy of Dermatology certifies that this educational activity has been recognized for 2 hours of AAD Category I credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

ACKNOWLEDGMENTS

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Joy Wan, M.D., M.S.C.E.
Albert C. Yan, M.D.

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CASE: 1 **NOTE:** Right cheek

AGE: 8 years **GENDER:** Female

PRESENTERS: Lauren Mihailides M.D. and James Treat M.D.

HISTORY:

Our patient originally presented at 21 days of life with a S2 segmental hemangioma involving her right cheek. At the time of presentation, she was using topical timolol on the area. Workup for PHACE syndrome including an MRI/MRA brain and neck, EKG, and echocardiogram were normal.

The patient was started on propranolol and titrated up to 2.5mg/kg/day. She was also treated with pulse dye laser (PDL) over 7 sessions from 2012 to 2013. The area improved and she was tapered off propranolol around 3 years of age and transitioned to timolol topically to residual areas. At 5 years of age, the hemangioma rebounded with fullness of her right cheek and soft palate. She was restarted on propranolol and later underwent an additional two sessions of PDL. The area has since improved but she required propranolol until age 8 when she was successfully tapered off without rebound.

MEDICATIONS: None (tapered off propranolol 2/2021)

PHYSICAL EXAMINATION: There is fullness of the right cheek with telangiectasias and areas of scarring with scattered telangiectasias on the upper lip.

IMAGING DATA:

(EKG 5/2012)

Normal sinus rhythm with a right ventricular conduction delay pattern (normal variant).

(Echocardiography, 5/2012)

Very small patent foramen ovale with left-to-right shunting. Right ventricular pressure estimate normal at 19 mmHg greater than the right atrial V wave. Aortic arch widely patent. There is no evidence of a coarctation of the aorta.

(MRI Brain and Orbits, 5/22/2012)

Right masticator space and cheek avidly enhancing lobulated lesion, in keeping with the clinical diagnosis of hemangioma, with prominent arterial feeders from the right external carotid artery. Unremarkable MRI of the brain and orbits. No additional hemangiomas are noted.

(MRA head and neck, 5/22/2012)

Unremarkable intracranial MRA. No arterial anomalies, stenoses, or aneurysms identified.

CASE: 1

DIAGNOSIS: Infantile hemangioma with rebound after therapy

DISCUSSION:

Infantile hemangiomas are the most common tumor in childhood, occurring in approximately 4% of children, and are subdivided into superficial, deep, and mixed subtypes depending on their location within the skin. Infantile hemangiomas generally proliferate in two stages, early and late, and then involute slowly. Beta blocker medications (topical timolol and oral propranolol) have become the mainstay of treatment for infantile hemangiomas that require treatment due to size, location, or other factors such as ulceration risk. The mechanism through which beta blockers treat hemangiomas is unknown, but likely effects angiogenesis and vasoconstriction.

Infantile hemangiomas typically meet their full growth potential by 12 months of age. However, there are reports of hemangiomas growing beyond 12 months of age, including after tapering of propranolol. In one study by Frieden *et al* in 2016, of 997 patients with infantile hemangiomas treated with propranolol, rebound growth was seen in 231 patients (25.3%) with the average age at initial rebound being 17.1 months. Certain patient factors were possibly associated with higher risk of rebound, including female gender, earlier age at propranolol discontinuation, location on head and neck, segmental pattern, and presence of a deep component; multivariate analysis revealed predictive associations of rebound with female gender and deep hemangiomas. In a smaller study by Khamaysi *et al* in 2021, 24 patients (11.7%) rebounded after stopping propranolol. This study found no patient or hemangioma-specific factors to be predictive of rebound in multivariate analysis.

The overall cause of rebound growth of hemangiomas is unclear. Rebound growth of hemangiomas is more commonly seen when propranolol is tapered quickly or discontinued prior to 9 months of age. In our patient, her female gender, facial location, deep component, segmental distribution, and location on the head and neck may have contributed to her multiple episodes of rebound growth despite slower tapering of propranolol and multiple sessions of pulse dye laser.

REFERENCES:

Shah SD, Baselga E, McCuaig C, et al. Rebound growth of infantile hemangiomas after propranolol therapy. Pediatrics. 137(4):e20151754-e20151754, 2016.

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CASE: 2 **NOTE:** Trunk, extremities, face, groin

AGE: 12 years **GENDER:** Male

PRESENTERS: Claire Hannah M.D. and Marissa J. Perman M.D.

HISTORY: Our patient is a citizen of the United Arab Emirates who presented for evaluation of a chronic rash that was previously biopsied and diagnosed as pityriasis lichenoides chronica (PLC). His past medical history is notable for unilateral renal agenesis. He first developed scaly, eroded papules and hypopigmented plaques on the trunk and extremities 5 years ago, which progressed to involve the face and groin. The lesions are occasionally pruritic and associated with a burning sensation. After a skin biopsy revealed findings consistent with PLC, he was treated with various medications including high-potency topical corticosteroids, topical calcineurin inhibitors, oral erythromycin, azathioprine, and a brief course of phototherapy. None of these therapies led to symptomatic or clinical improvement, which prompted his family to seek a second opinion at CHOP. At his initial visit, he was noted to have extensive involvement of the trunk, extremities, and face. Our dermatopathologists reviewed his prior skin biopsy and also described findings consistent with pityriasis lichenoides. He was started on weekly subcutaneous methotrexate with folic acid. At his follow up visit 2 months later, his rash had significantly improved. There was residual hyperpigmentation, but no new or active scaly papules or plaques.

MEDICATIONS: Tacrolimus ointment, clobetasol ointment, oral erythromycin, azathioprine, methotrexate with folic acid.

PHYSICAL EXAMINATION: The patient has innumerable pink, scaling and eroded papules scattered diffusely on the face, neck, trunk, extremities, and groin. There are many hypopigmented, scaling patches concentrated on the face and trunk.

LABORATORY DATA:
CBC, CMP: normal
LDH, normal
Quantiferon gold, negative

HISTOPATHOLOGY:
(9/24/19, right abdomen) The biopsy shows hyperkeratosis and parakeratosis of the stratum corneum. There are interface changes including lymphocytes at the dermal-epidermal junction, as well as vacuolar degeneration of basal keratinocytes. Lymphocyte exocytosis is present in the epidermis. There is a mild mixed perivascular inflammatory infiltrate in the upper dermis. CD30 highlights scattered cells in the specimen. These findings are consistent with pityriasis lichenoides.

CASE: 2

DIAGNOSIS: Pityriasis lichenoides chronica

DISCUSSION:

Pityriasis lichenoides (PL) is an uncommon, inflammatory papulosquamous disorder that can present as an acute, ulcerative eruption called pityriasis lichenoides et varioliformis acuta (PLEVA), or as a chronic, nonulcerative variant called pityriasis lichenoides chronica (PLC). PLC may develop at any age but is mostly likely to occur in young adults and children. Patients with PLC present with gradual onset of multiple scaly, erythematous to brown papules on the trunk, buttocks, and extremities. In contrast, patients with skin of color more often develop widespread hypopigmented macules and demonstrate increased facial involvement. The eruption is usually asymptomatic, though can be associated with pruritus. Healed primary lesions are nonscarring but can result in persistent pigmentary alteration.

The pathogenesis of PLC is poorly understood though may represent a hypersensitivity response to infection or a primary lymphoproliferative disorder. PLC has rarely been reported to occur in association with drug exposure. Diagnosis is often suspected based upon clinical appearance but should be confirmed with skin biopsy when possible. Characteristic pathologic features of PLC include parakeratosis, mild spongiosis, minimal lymphocyte exocytosis, minimal vacuolar change, perivascular and lichenoid lymphohistiocytic infiltrate in the superficial dermis, and few extravasated erythrocytes in the papillary dermis.

Treatment of PLC depends on the severity of disease. Because this disease is often asymptomatic and self-limited, treatment is not mandatory but may help to improve visible signs of disease. First-line therapies include topical corticosteroids, oral antibiotics (e.g., tetracyclines, erythromycin), and narrowband ultraviolet B phototherapy or natural sunlight in the spring and summer. These therapies are often well-tolerated and effective in achieving sustained remission. Second-line therapies for refractory disease include topical tacrolimus, methotrexate, dapsone, systemic glucocorticoids, and cyclosporine. Patients with PLC typically exhibit a relapsing and remitting course that lasts for months to years. PLC is considered a benign disease but can very rarely be associated with underlying hematologic and solid organ malignancies. In children, this association appears to be even rarer. Cancer screening beyond age-appropriate measures is not typically recommended.

REFERENCES:

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Zang JB, Coates SJ, Huang J, et al. Pityriasis lichenoides: Long-term follow-up study. Pediatr Dermatol. 35(2):213, 2018.

Bellinato F, Maurelli M, Gisondi P, et al. A systematic review of treatments for pityriasis lichenoides. J Eur Acad Dermatol Venereol. 33(11):2039, 2019.

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CASE: 3 **NOTE:** Entire body

AGE: 14 years **GENDER:** Male

PRESENTERS: Daniel J. Lewis M.D. and Leslie A. Castelo-Soccio M.D., Ph.D.

HISTORY: Our patient is a 14-year-old boy who was noted at birth to have a collodion membrane as well as ectropion, eclabium, and contractures with partial amputation of digits. He required admission for the first six months of his life, during which his collodion membrane shed followed by the development of hardened, plate-like skin. As a young child, he exhibited diffuse skin redness and fissuring, sparse hair, recurrent middle ear impaction, missing teeth, heat intolerance, and severe keratoderma causing impaired ambulation. He also experienced a number of complications, including skin infections treated with oral antibiotics, dilated cardiomyopathy, failure to thrive requiring a gastrostomy tube, and keratitis prompting surgery of the lower eyelids.

At age 8, he presented to an outside hospital and underwent diagnostic genetic testing, which revealed a homozygous *ABCA12* mutation. His consanguineous parents, who are first cousins, also underwent genetic testing; each was found to have a heterozygous *ABCA12* mutation. After diagnosis, the patient was treated with isotretinoin for two years prior to presenting to our clinic, where his skin condition has been managed with multiple courses of isotretinoin and acitretin as well as topical therapies with significant improvement in his erythema and scaling. He currently remains on acitretin and topical agents. He has also undergone surgical intervention to release his finger contractures and release his ears from the scalp, as well as recanalization of his lacrimal ducts. He follows with Endocrinology and is maintained on growth hormone for short stature.

MEDICATIONS: Acitretin, hydroxyzine, tazarotene cream, triamcinolone ointment, hydrocortisone ointment, urea cream, petroleum jelly, erythromycin ophthalmic ointment

PHYSICAL EXAMINATION: There is erythroderma with overlying white scale on head, trunk, arms and legs. There are sparse hairs on the scalp with evidence of scarring, and the earlobes and helices are fused to the scalp. There is bilateral ectropion and eclabium with surrounding taut skin. There are also missing teeth. There is palmoplantar keratoderma in addition to right-sided fused fingers, finger contractures, and distal truncation.

LABORATORY DATA:
ABCA12 genetic testing (GENEDx): Apparent homozygous for L487X mutation
NIPAL4 genetic testing (GENEDx): Negative
CYP4F22 genetic testing (GENEDx): Negative
ALOX12B gene testing (GENEDx): Heterozygous for P296T variant

CASE: 3

DIAGNOSIS: Harlequin ichthyosis

DISCUSSION:

Harlequin ichthyosis (HI) is the most severe inherited form of ichthyosis. It is an autosomal recessive disorder due to mutations in the *ABCA12* gene, which encodes a protein that transports epidermal lipids across cell membranes. Dysfunctional *ABCA12* prevents the formation of lipid bilayers within the stratum corneum, yielding massive hyperkeratosis and a disrupted permeability barrier. Diagnosis is often based on appearance at birth and confirmed by genetic testing.

Individuals with HI are usually born prematurely and present at birth with a collodion membrane. This shiny, transparent membrane is shed shortly after birth, resulting in the formation of hard, thickened yellow armor-like plates covering the entire body separated by deep, red fissures. Additional dermatologic findings include eclabium and ectropion due to surrounding taut skin. The ears may be absent or hypoplastic, as may the digits in addition to exhibiting flexion contractures. The compromised skin barrier also results in excessive water loss, electrolyte abnormalities, temperature dysregulation, and an increased risk of life-threatening infections. The thickened skin can restrict ventilation, and its increased metabolic activity can lead to cardiomyopathy as well as failure to thrive and short stature.

In the past, HI was uniformly fatal. Although there remains a high mortality rate among neonates due to respiratory insufficiency or sepsis, the majority of affected individuals now live beyond the neonatal period. Over the past two decades, intense neonatal supportive care and early systemic retinoid therapy such as acitretin or isotretinoin have markedly prolonged survival and improved quality of life.

REFERENCES:

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Singh S, Bhura M, Maheshwari A, et al. Successful treatment of harlequin ichthyosis with acitretin. Int J Dermatol. 40(7):472, 2001.

Thomas AC, Cullup T, Norgett EE, et al. ABCA12 is the major harlequin ichthyosis gene. J Invest Dermatol. 126(11):2408, 2006.

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CASE: 4 **NOTE:** Face, trunk, extremities, buttocks

AGE: 18 months **GENDER:** Male

PRESENTERS: Diego R. Dasilva M.D., Mary Larijani M.D., Ilka Arun Netravali M.D., Ph.D., and Patrick McMahon, M.D.

HISTORY: Our patient presented at 3 months of age with a history of parental consanguinity and micrognathia s/p mandibular distraction with titanium for failure to thrive with persistent peripheral eosinophilia and a diffuse eczematous eruption involving the face, trunk, and extremities. A prior skin biopsy was non-diagnostic and did not show clear evidence of an eczematous process, nutritional deficiency, or congenital ichthyosis. He was treated with gentle skin care, emollients, and topical steroids with moderate improvement. Immunology was consulted and identified a hypogammaglobulinema with low B cell count, but whole exome sequencing was unremarkable. He was subsequently started on IVIG and transitioned to Hizentra (immunoglobulin subcutaneous). Rash waxed and waned with the above therapy, but itching became intractable. At 4 months of age, dupilumab was started at 6 mg/kg every two weeks with impressive response after one month of treatment. Patient's dermatitis has remained relatively clear with mild flares responding to topical steroids while on the dupilumab.

MEDICATIONS: Tacrolimus ointment, triamcinolone ointment, mupirocin ointment, dupilumab

PHYSICAL EXAMINATION: Eczematous plaques, xerosis and excoriations were noted on face, trunk, extremities, buttocks at time of initial presentation. Mild thin eczematous papules are present on cheeks, trunk, extremities at most recent office visit.

LABORATORY DATA:
Copper, normal; Zinc, normal
HSV PCR, negative
Whole exome sequencing, normal
Bone marrow and lymph node biopsies, normal
IgE, normal**; IgG (12); IgA (<6); IgM (5);**
CBC: leukocytosis to 20s-30s; B-cell count (140); Eosinophilia to 22.9 (60% total)

HISTOPATHOLOGY:
(11/18/2019) Per outside hospital records the skin biopsy demonstrates focal parakeratosis, mild dyskeratosis, focal hemorrhage and mild perivascular lymphocytic inflammation. No evidence of eosinophils mentioned in the pathology report.

CASE: 4

DIAGNOSIS: Severe atopic dermatitis in an infant treated with dupilumab

DISCUSSION:

Until recently, systemic treatments other than prednisone for the treatment of severe atopic dermatitis (AD) in pediatric patients have all been off-label. As recently as five years ago, a poll of North American pediatric dermatologists showed that the most common first-line systemic medications for pediatric AD were methotrexate (30%) or cyclosporine (45%), with use of methotrexate or mycophenolate mofetil for long-term disease control. A major deterrent to using these systemic medications is the concern for severe adverse effects.

Dupilumab, an IL-4Rα and IL-13Rα antagonist, is the first targeted treatment for severe AD and was FDA-approved for adults 18 years of age and older in 2017. In March 2019, the FDA expanded approval to include adolescents 12 to 17 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. In May 2020, approval was granted for children 6 to 11 years of age. These approvals were based on data from pivotal phase 3 clinical trials investigating dupilumab monotherapy in adolescent patients followed by those of younger children with moderate-to-severe AD, which demonstrated clinically meaningful improvements in signs and symptoms of the disease along with important quality of life benefits. Adverse events mirrored those documented in adults including increased rates of mild-to-moderate conjunctivitis (10%) and single-digit rates of injection-site reactions. As a counterbalance to these adverse events, pediatric patients receiving dupilumab experienced significantly reduced rates of skin infections.

Use in infants as young as 4 months is off-label but case reports as well as our anecdotal use demonstrate its safety and effectiveness in treating severe AD. In an abundance of caution, for this patient, we obtained a baseline CBC with diff and CMP and repeated these studies every 2-3 days as an inpatient. Dosing is highly variable without established guidelines, ranging from 4 to 15.5 mg/kg every two weeks in reports. We considered increasing this patient's dose beyond 6 mg/kg, but did not given his adequate response.

REFERENCES:

Siegfried EC, Igelman S, Jaworsk JC, et al. Use of dupilimab in pediatric atopic dermatitis: Access, dosing, and implications for managing severe atopic dermatitis. Pediatr Dermatol. 36:172–176, 2019.

Simpson EL, Paller AS, Siegried EC, et al. Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, PlaceboControlled, Double-Blind, Parallel-Group, Phase 3 Study. 27th European Academy of Dermatology and Venereology (EADV) Congress: Abstract D3T01.1L. Presented September 15, 2018.

Totri CR, Eichenfield LF, Logan K, et al. Prescribing practices for systemic agents in the treatment of severe pediatric atopic dermatitis in the US and Canada: The PeDRA TREAT survey. J Am Acad Dermatol. 76:281‐285, 2017.

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CASE: 5 **NOTE:** Face

AGE: 13 years **GENDER:** Female

PRESENTERS: Neha N. Jariwala M.D., Michele Khurana, M.D., and James Treat M.D.

HISTORY: Our patient is a 13-year-old female with extensive and recalcitrant atopic dermatitis. Her disease was refractory to topical therapies and methotrexate. She was started on dupilumab in 2019. She initially noted significant improvement on her trunk and extremities, but soon after developed a facial and neck rash with erythema and pruritus. She was treated with topical steroids, tacrolimus and oral cyclosporine with no benefit. Dupilumab was discontinued and she was treated with fluconazole daily for 3 days and then weekly fluconazole maintenance therapy for 2 months, with resolution of the facial rash. She was re-started on methotrexate for her atopic dermatitis and then re-transitioned to dupilumab last year with excellent success. Several months after resuming dupilumab, the patient experienced a flare of her facial dermatitis and fluconazole dosing was increased to three times weekly for a week with improvement of her symptoms.

MEDICATIONS: Tacrolimus ointment, triamcinolone ointment, mupirocin ointment, fluconazole, dupilumab

PHYSICAL EXAMINATION: There are eczematous patches on the face, neck, and upper trunk.

LABORATORY DATA:
Patch testing with positivity to bacitracin.

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 5

DIAGNOSIS: Dupilumab-associated facial and neck dermatitis

DISCUSSION:

Dupilumab is the only FDA approved systemic therapy for moderate to severe atopic dermatitis. It was approved for adolescents 12 years and older in 2019 and for children over the age of 6 years in May of 2020. Common side effects include conjunctivitis and injection site reactions. However, recently, several studies have reported an associated facial and neck dermatitis, as our patient experienced. There are estimates that as many as 10% of adults and 29% of children on dupilumab experience this side effect. Patients often present with erythema and pruritus of the face and neck usually within months of starting dupilumab.

The pathophysiology of dupilumab-associated facial and neck dermatitis is not fully elucidated, but it is thought to be related to unmasking allergic contact dermatitis, rosacea with increased colonization by *Demodex*, psoriasis, or Malassezia-related seborrheic dermatitis. Proposed mechanisms involve IL-4 receptor blockade related shifts to a Th1 activated immune response.

Given the seborrheic distribution and association with Malassezia, proposed treatments include primarily antifungal therapy. Some experts empirically treat all of their dupilumab patients with ketoconazole cream. At our institution, oral antifungal therapy is the mainstay of treatment, as utilized in this patient. Interestingly, recent literature suggest that antifungal therapies also have anti-inflammatory properties, and therefore, the specific mechanisms which contribute to clinical improvement remain unclear.

REFERENCES:

Bax CE, Khurana, MC, Treat JR et al. New-onset head and neck dermatitis in adolescent patients after dupilumab therapy for atopic dermatitis. Pediatric Dermatology. 00:1–5, 2020.

Muzumdar S, Zubkov M, Waldman R, et al. Characterizing dupilumab facial redness in children and adolescents: a single-institution retrospective chart review. J Am Acad Dermatol. 83(5):1520-1521, 2020.

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CASE: 6 **NOTE:** Abdomen, back, neck

AGE: 13 years **GENDER:** Female

PRESENTERS: Ilka Arun Netravali M.D., Ph.D., Arianna Yanes M.D., and Marissa Perman M.D.

HISTORY: Our patient is a 13-year-old female well known to our clinic with junctional epidermolysis bullosa (JEB), generalized intermediate (non-Herlitz) type (with collagen 17 mutation) with history of recurrent MSSA, MRSA, and pseudomonas colonization. She presented with a new, asymptomatic rash on her neck, trunk, and extremities. The rash initially appeared several years prior and was gradually spreading. Coconut oil emollients, a potential source of contact dermatitis, were discontinued and topical triamcinolone 0.025% and 0.1% ointments were tried without significant improvement. Family felt there was some improvement in areas exposed to a heat lamp. Initial biopsy from the lower back was notable for follicular induction and focal Pityrosporum. A trial of pulse fluconazole for 4 weeks in addition to a 1:1 mixture of ammonium lactate 12% and fluocinolone 0.01% ointment were ineffective, and the rash continued to progress at two month follow up. Repeat biopsy at that time corroborated follicular induction.

MEDICATIONS: Mupirocin ointment, gentamicin ointment, gentian violet, chlorhexidine, Vashe hypochlorous acid, 1:1 mixture of ammonium lactate 12% and fluocinolone 0.01% ointment, pulse fluconazole for 4 weeks

PHYSICAL EXAMINATION: On the neck, trunk, and proximal upper and lower extremities, there are innumerable discrete and coalescing pink and red stippled papules and linear hyperkeratotic plaques. There is lichenification noted on the shoulders. Eruption on the posterior neck and upper back is less confluent.

LABORATORY DATA: Not applicable

HISTOPATHOLOGY:
(10/12/2020, right lateral back, 3 mm shave biopsy; 12/30/2020, right lateral back, left middle back, right neck, 4 mm punch biopsies x3): The biopsies show features of follicular induction, with anastomosing strands of epithelium emanating from the epidermis in association with an increased number of sebaceous glands and features of myxoid perifollicular mesenchyme. These histologic features extend throughout the specimen and are observed in areas with and without paucicellular subepidermal blisters, as well as in areas with dermal fibrosis, consistent with early scar formation. PAS stained sections from the shave biopsy demonstrate focal Pityrosporum organisms, likely an incidental finding.

CASE: 6

DIAGNOSIS: Follicular induction in junctional epidermolysis bullosa (JEB)

DISCUSSION:

Epidermolysis bullosa (EB) are genetic disorders defined by skin fragility due to mutations in genes encoding cell adhesion proteins. JEB is an autosomal recessive EB subtype in which dermal-epidermal adhesion is reduced due to deficiency in anchoring filament proteins that link keratin to the basement membrane. The histological correlate is a non-inflammatory blister at the lamina lucida underlying a spectrum of phenotypes. In the generalized severe form, exuberant skin and mucosal granulation tissue, failure to thrive, and respiratory failure portend a poor prognosis. In contrast, in the generalized intermediate form due to *Collagen XVII* (*COL17*) mutations, as in our patient, blistering may improve, but can remain diffuse, healing with atrophy and pigmentary alteration.

Follicular induction is a histological phenomenon in which an altered dermal stroma “tricks” the epidermis into believing it is younger than it is, and to generate primitive hair follicles and associated sebaceous glands. The process mimics embryologic development and is classically described in association with dermatofibromas. It has also been reported in conjunction with a wide range of neoplasms and reactive conditions including neurofibroma, hemangioma, basal and squamous cell carcinoma, cutaneous metastases, and viral warts.

This case is the first report of follicular induction in JEB, and in any inherited or acquired bullous disorder. The hyperkeratotic plaques we observe are also unique, as skin surface change has not been described with induction. While induction is a reaction to fibrohistiocytic (in dermatofibromas) and/or vascular proliferation in the dermis, these are absent in our patient, and its trigger and clinical significance remain unclear.

Recent work shows that COL17 is expressed beyond hemidesmosomes, in hair follicle stem cells (HFSCs), where it regulates epidermal proliferation. Its degradation in HFSCs triggers their terminal differentiation into keratinocytes at the expense of follicle maintenance, simultaneously promoting interfollicular epidermal hypertrophy and follicular miniaturization. What then is driving follicular induction in our patient with homozygous *COL17* deficiency? One hypothesis is that our patient has had somatic correction of her inherited *COL17* mutation (i.e., revertant mosaicism), as seen in other cases of JEB, restoring protein function in discrete patches with follicular induction. Genomic analysis and immunostaining studies of COL17 will provide additional insight.

REFERENCES:

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CASE: 7 **NOTE:** Abdomen, lower back, thighs

AGE: 13 years **GENDER:** Male

PRESENTERS: Heather Milbar M.D., M.P.H., Robert Smith M.D., Marissa Perman M.D., and Aditi S. Murthy M.D.

HISTORY: Our patient presented for evaluation of multifocal painful abdominal nodules. The patient has a history of type 1 diabetes mellitus (T1DM), diagnosed three years prior to presentation. Six months prior to presentation, he began to develop deep, painful nodules at the sites of insulin injections. These nodules arose hours-to-days following an insulin injection, persisted for many months, and occurred at all anatomic regions where the injections were performed including the abdomen, back, and thighs. Following the development of these nodules, despite compliance with his diabetic medications, his glycemic control gradually worsened. He was ultimately admitted to the hospital with diabetic ketoacidosis. He denied any history of fevers, joint pains, weight loss, oral ulcers, abdominal pain, diarrhea, or dyspnea.

MEDICATIONS: Dexmethylphenidate, omeprazole, insulin aspart

PHYSICAL EXAMINATION: Physical exam demonstrates numerous tender subcutaneous nodules at insulin injections sites of the abdomen, lower back, and thighs. Some of the nodules have overlying erythema.

LABORATORY DATA:
Hemoglobin A1c, 11.3% (nl 3.8-5.9%)
POC Glucose, 330 (nl 70-106mg/dL)

IMAGING DATA: None

HISTOPATHOLOGY:
(9/27/19, left and right abdominal wall) The biopsies show features of a predominantly lobular lymphohistiocytic panniculitis. Some areas of the specimen also demonstrate a minority component of septal panniculitis with lymphohistiocytic inflammation. Focal necrosis of the adipose tissue is identified. Polarizable material is not identified in these sections.

CASE: 7

DIAGNOSIS: Insulin-induced localized lobular panniculitis

DISCUSSION:

The histopathologic differential for a lobular panniculitis is broad and includes connective tissue disease (e.g., lupus profundus), malignancy (subcutaneous panniculitis-like T-cell lymphoma), infection (e.g., atypical mycobacteria), reactive processes (e.g., erythema induratum), inflammatory processes (e.g., lipodermatosclerosis), traumatic processes (e.g., cold panniculitis, post-steroid panniculitis), and endocrinologic causes (e.g., pancreatic panniculitis). A multi-disciplinary evaluation for this patient did not identify a systemic cause of panniculitis, such as inflammatory bowel disease, pancreatic disease, malignancy, connective tissue disease, or systemic infection. Traumatic panniculitis was considered less likely, as injection of other substances did not result in the formation of nodules. This patient was ultimately discharged with a continuous insulin pump for management of his glucose and oral indomethacin for management of his panniculitic nodules. Four months after presentation, his prior nodules had resolved, though he continued to have an inflamed painful nodule at the site of his continuous pump. His Hemoglobin A1C had started to improve, but remained elevated at 10.7%.

Insulin-induced injection site panniculitis is rare. This is distinct from localized injection site lipohypertrophy, which is a well described side effect of long-term insulin injections. The mechanism for medication-induced injection-site panniculitis is not fully known. In T1DM, it is hypothesized that serum insulin autoantibodies bind with the injected insulin to form IgG immune complexes. Subcutaneous macrophages recognize and phagocytize these immune complexes, triggering a type III hypersensitivity reaction, which manifests clinically as an inflammatory panniculitis. This hypothesis is supported by the fact that this patient experienced worsening glycemic control, suggesting that his insulin was broken down prior to effective metabolic absorption. Other injectable medications, such as glatiramer acetate, have been described to cause similar inflammatory injection-site panniculitides. After the inflammatory panniculitic nodules resolve, patients are left with hyperpigmented atrophic patches resembling lipoatrophy.

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Philadelphia Dermatological Society
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CASE: 8 **NOTE:** Abdomen, back, legs, feet

AGE: 15 years **GENDER:** Female

PRESENTERS Stephanie Florez-Pollack M.D. and Melinda Jen M.D.

HISTORY: Our patient initially presented at 4 years of age for evaluation of a hypopigmented patch on her abdomen and left leg diagnosed as nevus depigmentosus. At her initial visit, she was noted to have a few benign appearing nevi within the area of depigmentation. Over the following ten years, multiple new nevi appeared within the depigmented patch and in other areas of the body, with multiple of them appearing clinically atypical. Several of these were subsequently biopsied and showed Spitz nevi with atypia, atypical Spitz nevi, dysplastic Spitz nevi, and combined nevi with Spitz features. At age 14, several clinically atypical nevi were biopsied from within the depigmented patch, and 5 had loss of BAP1 staining in lesional melanocytes. Genetic testing for BAP1 mutations was performed on blood and revealed a heterozygous pathogenic variant of BAP1.

MEDICATIONS: None

PHYSICAL EXAMINATION: Segmental depigmented patch extending from the left lower abdomen and left lower back with sharp midline demarcation extending to the entire left leg with some sparing of the distal dorsal foot. There are multiple brown, red, dark brown, and pink-brown macules and papules scattered throughout the depigmented area.

LABORATORY DATA:
Sequence analysis and deletion/duplication testing of BAP1:
Likely Pathogenic variant, c.375+2T>A (Splice donor), was identified.

HISTOPATHOLOGY:
(12/4/19) A) Left dorsal foot; B) Left lateral abdomen; C) Left central abdomen; E) Left knee; F) Left heel: The epidermis demonstrates hyperplasia with nested and single melanocytes in the epidermis and dermis that have epithelioid and spindled shapes, and demonstrate increased nuclear sizes and distinct nucleoli. Pagetoid melanocytosis is present. A second population of small round melanocytes reminiscent of those seen in congenital pattern melanocytic nevi are also identified. P16 was mostly retained in the lesional melanocytes. There was loss of staining of BAP1 in the lesional melanocytes. Melan-A/PHH3 stained sections confirm the histologic impression. The sections were extensively examined, and a single lesional dermal mitotic figure was identified.

D) Skin, left abdomen medial: The epidermis demonstrates hyperplasia with nested and single melanocytes in the epidermis and dermis that have epithelioid and spindled shapes, and demonstrate increased nuclear sizes and distinct nucleoli. Nested melanocytes are present at the bases of the rete ridges and here is bridging between rete nests. The sections were extensively examined and lesional dermal mitotic figures were not identified. Focal pagetoid spread of melanocytes is identified in the epidermis. Melan-A/PHH3 stained sections confirm the histologic impression. There is a zone of uninvolved tissue at all margins of the sections examined.

CASE: 8

DIAGNOSIS: BAP1 tumor predisposition syndrome with multiple atypical nevi

DISCUSSION:

BAP1 tumor predisposition syndrome (TPDS) is a hereditary cancer syndrome caused by mutations in the BAP1 (BRCA1-associated protein 1) tumor suppressor gene. Germline mutations in BAP1 are associated with an increased risk for cancers such as uveal melanoma, malignant mesothelioma, cutaneous melanoma, and renal cell carcinoma. Most individuals with a BAP1 mutation develop multiple non-cancerous cutaneous melanocytic neoplasms that resemble atypical Spitz tumors and dermal nevi but are clinically, histologically, and genetically different. It has been estimated that up to 85% of individuals with a mutation will develop cancer by 65 years of age, and an earlier age of onset for cancer has been observed compared to that seen in the general population.

Our patient did not have a family history of BAP1 tumor predisposition syndrome or associated malignancies. Parental and sibling testing showed no BAP1 mutation . Given the patient's segmental depigmentation and clustering of BAP1 inactivated tumors within the depigmented area, there is a possibility of mosaicism of BAP1 loss within the area. Unfortunately, tissue BAP1 testing of affected, depigmented skin compared to normal background skin is not available.

Management of patients with a BAP1 mutation is centered around cancer prevention and surveillance. This includes annual physical examination, annual dilated eye exam, ophthalmic imaging by an ocular oncologist beginning at age 11 years, and annual dermatology full body skin exam. No current screening for clear cell renal carcinoma or malignant mesothelioma is recommended. While mutations may occur de novo, screening of first degree relatives is recommended. Genetic counseling should be performed for patients as part of family planning.

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CASE: 9 **NOTE:** Palms, soles, finger and toenails, and hair

AGE: 26 months **GENDER:** Male

PRESENTERS: Ashley Clark M.D. and Leslie Castelo-Soccio M.D., Ph.D.

HISTORY: Our patient presents with thickened nails. Symptoms first developed around 2 months of age with yellowing and progressive thickening of the nails. Additionally, he had two episodes of paronychia treated with incision and drainage as well as oral cephalexin. His hair is notably blonde and sticks straight up. His father had similar hair as an infant, as well as a history of nail and feet issues, many cysts, a missing adult tooth, and hidradenitis.

MEDICATIONS: Urea cream, vinegar soaks, mupirocin ointment

PHYSICAL EXAMINATION: There are multiple small hyperkeratotic papules on the knees. He has conical, hyperkeratotic yellow nails on all toes and all fingernails. He does not have changes in the oral cavity. His palms and soles are without hyperkeratosis or callous. His hair is blonde and wiry in texture and does not lay flat.

LABORATORY DATA:
Genetic testing shows that the patient is heterozygous for a pathogenic variant (p.Met88Arg, ATG>AGG) in the KRT17 gene (c.263, T>6 in exon 1), which is consistent with the diagnosis of KRT17-related disorder.

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 9

DIAGNOSIS: Pachyonychia congenita and uncombable hair syndrome

DISCUSSION:

Pachyonychia congenita (PC) is a rare autosomal dominantly inherited genodermatosis and consists of two main types. PC-1 (Jadassohn-Lewandowsky type), the most common variant, is associated with mutations in genes coding keratins K6a and K16. PC-2 (Jackson-Lawler type) is a rare variant that has been linked to mutations in keratin K6b and K17. Clinically, PC-1 presents with hyperkeratotic palms and soles, hypertrophic nail dystrophy with thickened brown-gray nail plates, follicular hyperkeratosis, and leukokeratosis of the oral mucosa. PC-2 patients present with findings similar to those with PC-1, with the additional findings of natal teeth, steatocystoma multiplex, epidermal inclusion cysts, and vellus hair cysts.

Mutations in keratins K6a, K6b, K16, and K17 are responsible for inducing PC. In our patient, a pathogenic mutation in K17 was found. Many of these mutations occur at the end of the helical rod domains of keratin leading to a disruption of normal keratin filament assembly. Histologically, the keratotic lesions on both the palms, soles, and oral mucosa reveal acanthosis, hyperkeratosis, and parakeratosis. Treatment is primarily supportive. Options for the nails and keratotic plaques include urea, salicylic acid, mechanical abrasion, and nail plate removal. Cysts can be surgically excised. Systemic retinoids have been attempted with varying results.

Uncombable hair syndrome (UHS) also known as “spun glass hair syndrome,” or “pili trianguli et canaliculi,” is a rare anomaly of the hair shaft that occurs in children and improves with age. The syndrome is characterized by dry, frizzy, fair hair that stands away from the scalp in multiple directions, and is impossible to comb. In the majority of cases, UHS is an isolated condition, but can be observed with ectodermal dysplasias, retinopathia pigmentosa, juvenile cataract, and polydactyly. This condition is unrelated to PC and was also coincidentally demonstrated in our patient.

The clinical diagnosis of UHS can be confirmed by scanning electron microscopy analysis of hair shafts. Familial cases have been described, and recently mutations in genes related to trichohyalin production have been reported including *PADI3* (peptidylarginine deiminase 3), *TGM3* (transglutaminase 3), and *TCHH* (trichohyalin). No effective therapy is yet available.

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CASE: 10 **NOTE:** Trunk and extremities

AGE: 18 years **GENDER:** Male

PRESENTERS: Corinne Rauck M.D., Christina Del Guzzo M.D., Michele Khurana M.D., Aditi Murthy M.D., Albert Yan M.D., Patrick McMahon M.D., and James Treat M.D.

HISTORY: Our patient is an 18-year-old male with a past medical history of *C. difficile* infection presenting with a 2-week history of fever, malaise, abdominal pain, bloody diarrhea, and rash consisting of scattered pustules and pink plaques with hemorrhagic bullae on the trunk and extremities. The patient also reported weight loss, recurrent abdominal pain, and intermittent bloody diarrhea for the past 1 year. He reported recent travel to Maine and fresh water canoeing and denied any insect bites or new medications. Family history included two cousins with inflammatory bowel disease. During his admission, a colonoscopy showed findings consistent with inflammatory bowel disease. He was treated with tacrolimus ointment, mometasone ointment, systemic steroids, and infliximab with excellent response.

MEDICATIONS: Tacrolimus ointment, mometasone ointment, prednisone, infliximab

PHYSICAL EXAMINATION: Pink plaques with a gunmetal grey border and clustered hemorrhagic bullae and nodules are scattered on the distal thighs, shins, and calves. Pink papules and pustules are scattered on the neck and trunk. Pustules in posterior pharynx and mucosal lower lip.

LABORATORY DATA:
WBC, 25.2 K/uL, (3.9-6.8 K/uL)
Neutrophils %, 82.2%, (40.3-74.8%)
HGB, 10.5 g/dL, (13.5-17.5 g/dL)
Fecal calprotectin, 3,000 ug/g, (0-50) ug/g
Fibrinogen, 584 mg/dL, (172-471 mg/dL)
Tissue bacterial, fungal, and mycobacterial cultures, without growth

HISTOPATHOLOGY:
(9/1/19, Right Thigh) Ulceration with predominantly neutrophilic dermal and perivascular/periadnexal infiltrates. Comment: Sections show skin with an ulceration predominantly composed of sheets of degenerating neutrophils. There is periadnexal and perivascular involvement with infiltration through the vascular walls. No fibrinoid necrosis or dying neutrophils are located within the walls, and the extent of vascular involvement is not sufficient to support a vasculitic process away from the ulcer bed. AFB, GMS, PAS, and Gram stains are negative.

CASE: 10

DIAGNOSIS: Pustular pyoderma gangrenosum

DISCUSSION:

Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis often presenting with inflammatory pustules that evolve into ulcers with purple to gray rolled borders. Lesions are typically found on the lower extremities and trunk, and characteristically heal in a cribriform pattern with a tendency to leave cribriform scarring. PG is rare in childhood, with the peak incidence estimated to be between 40-60 years of age. PG is often associated with an underlying medical condition, most commonly inflammatory bowel disease, inflammatory arthritis, leukemia, myelodysplastic syndrome, or IgA paraproteinemia. In children specifically, the literature reports more than 40% of children with PG have underlying inflammatory bowel disease.

There are five clinical subtypes of PG including bullous, peristomal, vegetative, classic, and pustular. Pustular PG, as seen in our patient, is the subtype most commonly associated with inflammatory bowel disease. Pustular PG may present with many inflammatory pustules that do not always ulcerate but may exhibit healing in a cribriform pattern. Similar to the other subtypes, patients with pustular PG may exhibit pathergy.

The clinical differential diagnosis for pustular PG is broad including infectious, vascular, neoplastic, or other inflammatory etiologies. The histopathology will show a dense neutrophilic infiltrate. Early lesions can also show suppurative folliculitis and late lesions can have ulceration with epidermal necrosis. Management of pustular PG includes systemic workup for underlying disease and treatment with topical steroids, topical calcineurin inhibitors, intralesional steroids, systemic steroids, and/or tumor necrosis factor-alpha inhibitors. Alternative systemic treatment options include azathioprine, cyclosporine, cyclophosphamide, and intravenous immunoglobulin. Therapeutic goals also include controlling the contributing underlying disease.

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CASE: 11 **NOTE:** Cheeks, ears, abdomen, back

AGE: 10 years **GENDER:** Male

PRESENTERS: Junqian Zhang M.D., Ilka Arun Netravali M.D., Ph.D, and Leslie Castelo-Soccio M.D., Ph.D

HISTORY: Our patient is a 10-year-old male with a history of failure to thrive, eosinophilic colitis, esophageal strictures, and osteosarcoma who presented for evaluation of skin changes on the ears and increased freckling. The patient has had skin issues since birth, with report of red areas and visible blood vessels on his ears at an early age. His parents also noticed freckling of the nose, cheeks, and forehead as well as hyperpigmented macules and patches on the abdomen and back. He was previously diagnosed with osteosarcoma of the left lower femur at age 7 years, and was treated with chemotherapy and wide local excision with Van Nes rotationplasty repair. The patient has had ongoing irritant contact dermatitis associated with his left lower extremity prothesthesis.

MEDICATIONS: Mometasone ointment, sunscreen

PHYSICAL EXAMINATION: There are poikilodermatous changes on the ear helices and conchal bowls. Small hyperpigmented macules are present on the cheeks, nose, and forehead. Lightly hyperpigmented patches are scattered on the abdomen, back, and proximal upper extremities.

LABORATORY DATA:
Genetic testing shows a pathogenic variant in *RECQL4* (c.318delG; p.Gln107Serfs*7) and a variant of uncertain significance (c.2264G>A; p.Arg755Gln).

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 11

DIAGNOSIS: Rothmund-Thomson syndrome

DISCUSSION:

Rothmund-Thomson syndrome (RTS) is a rare genodermatosis that presents with photosensitivity and early-onset poikilodermatous skin changes in association with skeletal abnormalities, premature aging, and predisposition to cancer.

Initially described by August von Rothmund, a German ophthalmologist, in 1868 and further characterized by Matthew Thomson, a British dermatologist, it was not until 1957 that the current eponym was coined.

RTS is divided into two clinical subtypes. Both clinical subtypes present with poikilodermatous skin changes, short stature, sparse hair, and abnormalities of the teeth and nails. Cutaneous signs of photosensitivity leading to erythema and edema present as early as 3-6 months on the face, and then spread to affect the extensor surfaces and buttocks. Telangiectasias, dyspigmentation, and cutaneous atrophy progressively develop in these areas. In addition, patients may develop keratotic plaques on the extensor surfaces and the soles, which may be premalignant. RTS type I is also associated with juvenile cataracts while RTS type II is associated with skeletal anomalies and increased risk for osteosarcoma. Bi-allelic mutations in the DNA helicase *RECQL4* have been implicated in the pathogenesis of RTS type II, while mutations in *ANAPC1* have recently been associated with RTS type I.

Multidisciplinary management is required for patients with RTS. Cutaneous poikiloderma can be improved with pulse-dye laser therapy. Sun protection/avoidance and regular screening exams for skin cancer are recommended. Non-dermatologic care includes screening for osteosarcoma and monitoring and treatment for subcapsular cataracts, periodontal disease, and skeletal anomalies. Although cutaneous signs of accelerated aging are often present, lifespan of patients with RTS is not altered.

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CASE: 12 **NOTE:** Left neck, chest, arm, thumb, and back

AGE: 16 years **GENDER:** Male

PRESENTERS: Brittany U. Oliver M.D., Colleen Cotton M.D., Warren Heymann M.D., Albert Yan M.D., and James Treat M.D.

HISTORY: Our patient presented at 14 years of age for evaluation of a birthmark involving the left neck, upper chest, back, and arm extending to the thumb. The lesion had not changed in size or appearance since birth. The patient reports intermittent pain localized to the birthmark with physical exertion accompanied by worsening numbness in the left thumb. He also notes purple discoloration of the lesion when exposed to cold temperatures. He does not have a history of café-au-lait spots or freckling but is incidentally noted to have a single nevus spilus. He underwent an echocardiogram due to his pain and this was normal.

MEDICATIONS: No relevant medications

PHYSICAL EXAMINATION: There are segmental vasoconstricted patches on the left face, left neck, upper chest, left arm down the forearm and involving left thumb, and back with cutoff at midline with redness at the leading edge in multiple areas. Normal appearing surrounding skin is noted to become erythematous upon rubbing. He is also noted to have a 1 cm hyperpigmented patch with overlying darker brown macules on the right medial thigh.

Asymmetric upper extremities with the following measurements:
- Upper arm circumference: Left: 24.0 cm vs. Right: 24.5 cm
- Forearm circumference: Left: 22.0 cm vs. Right: 22.5 cm

LABORATORY DATA:
11/6/2019, genetics study from tissue: Missense GNA11 mutation (single base substitution C to T) in exon 4 and deemed to be a pathogenic somatic mutation.

Genetics study from blood: The mutation was not found in DNA examined from the blood.

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 12

DIAGNOSIS: Nevus vascularis mixtus (giant nevus anemicus) – *GNA11* mutation

DISCUSSION:

Nevus anemicus is a pale area of skin commonly found on the upper to mid trunk and consisting of well-defined, irregular patches which demonstrate pallor. This finding is due to congenital localized hypersensitivity of blood vessels to endogenous catecholamines, resulting in persistent vasoconstriction of affected skin. Lesions characteristically become imperceptible with pressure due to blanching of surrounding skin. Stroking or rubbing normal surrounding skin results in erythema, accentuating the lesion which remains pale.

Nevus anemicus may be seen as an isolated finding or may occur in association with several syndromes in the presence of other suggestive cutaneous findings. The missense mutation observed in our patient has previously been documented as a somatic mutation in patients with phakomatosis pigmentovascularis, congenital hemangiomas, overgrowth syndromes, and nevus vascularis mixtus. Nevus vascularis mixtus is a binary phenotype consisting of a nevus anemicus and telangiectatic nevus which may be associated with CNS abnormalities, most often cerebrovascular malformations. The variant seen in our patient has been previously documented to promote tumor growth, though with less potency than other *GNA11* mutations. Functional studies of this missense mutation suggest it results in increased activity of mitogen-activated protein (MAP) kinase. *GNA11* mutations have also been found in blue nevi, nevus of Ota, and uveal melanomas.

REFERENCES:

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CASE: 13 **NOTE:** Scalp, face, arms

AGE: 32 months **GENDER:** Male

PRESENTERS: Victoria Fang M.D., Ph.D. and Leslie Castelo-Soccio M.D., Ph.D.

HISTORY: This patient was born at 39/2 weeks via C-section and presented at 7 months of age with hypotrichosis of his scalp, eyebrows, and eyelashes. He was born without hair, eyebrows, or eyelashes, and started to grow very fine hair on scalp at 6 months of age. He regularly gets red and hot but does not sweat. Additionally he has an enlarged head and enlarged tongue, retrognathia, a scrotal dimple, and a history of atopic dermatitis. Family history is significant for absence of incisors in his mother, and eczema and hypohidrosis in his sister. At 9 months of age, he still had not grown any teeth, and had thick oral secretions resulting in difficulty swallowing food, requiring temporary feeding via NG tube. At 30 months of age, he has a total of 2 teeth, pointed in appearance.

MEDICATIONS: Mometasone ointment, hydrocortisone ointment

PHYSICAL EXAMINATION: The scalp has sparse, fine vellus hair. He is missing eyebrows, and has very sparse blond eyelashes. There are red scaly patches on the eyebrow and chin. There is mild white scale on the lower legs. There is slight wrinkling under the eyes. There is an indentation between the scrotal sacs at midline. At 30 months of age, he had 2 incisor teeth which are sharp and pointed in appearance.

LABORATORY DATA:
Genetic testing was positive for 1) hemizygous pathogenic variant in EDA (ectodysplasin-A) and 2) heterozygous pathogenic variant in WNT10A.

Loss of function variants in EDA gene are associated with X-linked ectodermal dysplasia, as it is involved in epithelial-mesenchymal interaction during ectodermal development. This patient had a Y310C mutation, which had not been previously reported, but mutations in nearby amino acids have been reported in association with ectodermal dysplasia. Additionally, the patient had a heterozygous WNT10A mutation (F228I variant) which has also been reported in association with oligodontia and ectodermal dysplasias.

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 13

DIAGNOSIS: Hypohydrotic ectodermal dysplasia

DISCUSSION:

Hypohydrotic ectodermal dysplasia (HED) is the most common of the more than 200 types of genetic ectodermal dysplasias. It is most frequently X-linked, although autosomal recessive and dominant forms exist. The X linked recessive form is associated with mutations in ectodysplasin-1 (EDA1). As the name suggests, this genetic disorder affects ectodermal structures such as the hair, teeth, skin, nails, and eccrine glands. It is characterized by the triad of hypotrichosis (of scalp, body, eyebrows, eyelashes), abnormal (peg-shaped) and missing teeth, and hypohidrosis. Newborns may have a collodion membrane and ichthyosis as well as febrile seizures due to anhidrosis and poor thermoregulation. The skin is often pale, dry, and hypopigmented, and about two-thirds of patients have atopic dermatitis.

Patients can also have dry eyes, airways, and mucosal membranes from defective exocrine glands. Infants can develop gastric reflux disease and feeding problems, as well as a hoarse or raspy voice. Some have dysmorphic facies with a prominent forehead, forehead bumps, rings under eyes, hypertelorism, epicanthic folds, everted nose, depressed nasal bridge, prominent lips, and prognathism. Immune deficiency can be associated with hypohidrotic ectodermal dysplasia in the variant with mutations in IKBKG/NEMO.

Diagnosis relies on physical exam, history, and genetic testing. Biopsy is not necessary, but a skin biopsy from the scalp or palm showing absence of eccrine glands can be seen in HED.

Treatment relies on controlling the child’s temperature with air conditioning of the home and school, hydration with cool liquids, cooling clothing, moisturizers for xerosis, careful dental care by pediatric dentistry and orthodontics, and prosthodontics for dentures or dental implants. Artificial tears are used to prevent cornea damage and saline sprays plus petrolatum are used to protect the nasal mucosa.

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CASE: 14 **NOTE:** Face, upper back, upper extremities

AGE: 13 years **GENDER:** Male

PRESENTERS: David Dunaway M.D. and Aditi Murthy M.D.

HISTORY: Our patient is a 13-year-old male with history of asthma who was first seen by dermatology in 2019. At that time he and his guardian reported 2 year history of rash on face, upper back and arms. At initial presentation, rash was reported to be worse in summer, especially July and August, but improved by triamcinolone 0.1% cream and ointment. A skin biopsy was performed in November 2019 with evidence of subtle interface dermatitis with superficial and deep dermal inflammation and the patient was referred to rheumatology who prescribed hydroxychloroquine. Since initiating systemic therapy, the patient has shown significant improvement in his cutaneous lesions, however experiences flares with prolonged sun exposure requiring topical steroids.

MEDICATIONS: Cetirizine, diphenhydramine, hydroxychloroquine, triamcinolone ointment

PHYSICAL EXAMINATION: On the lateral cheeks, upper back, and bilateral arms there are hyperpigmented flat papules, some with central atrophy and scale, coalescing into plaques.

LABORATORY DATA:
CBC and CMP were normal. UA was normal. ANA was negative.

IMAGING DATA: None

HISTOPATHOLOGY:
(10/29/19, right forearm) The biopsy shows subtle interface dermatitis and superficial and deep dermal inflammation. There are focal areas of the lower layers of the epidermis which demonstrate vacuolar degeneration of keratinocytes with associated dyskeratotic keratinocytes. The overlying epidermis demonstrates mild hyperkeratosis. There is superficial and deep perivascular predominantly lymphocytic inflammation which has some extension into the adnexal structures, PAS stained sections did not show fungal elements in the specimen, and demonstrate focal thickening of the basement membrane. Colloidal iron stain sections demonstrate focal areas of increased mucin in the dermis.

CASE: 14

DIAGNOSIS: Discoid lupus erythematosus

DISCUSSION:

Discoid lupus erythematosus (DLE) is a subset of chronic cutaneous lupus, and in adults is the most common form of chronic cutaneous lupus. The primary lesions are described as red scaly macules and papules that heal with pigmentary changes and scar. Lesions are most commonly found in photo-distributed areas including the scalp, forehead, central face, and neck. Of note, sunlight is thought to play a role in the pathogenesis of new lesions.

DLE in children is rare with fewer than 3% of patients developing DLE before 10 years of age. While anywhere from 0-28% of adults with DLE will later be diagnosed with systemic lupus erythematosus (SLE), it has been reported that almost 40% of children with DLE eventually will be diagnosed with SLE, with the greatest risk within the first year after DLE diagnosis. Children diagnosed with DLE require long term monitoring for development of systemic disease.

Treatment of DLE is multimodal and includes topical steroids, oral antimalarials, as well as vigilant sun protection. Due to the potential risk for irreversible retinopathy, the American Academy of Ophthalmology has recommended that patients beginning long-term hydroxychloroquine or chloroquine treatment have a baseline ophthalmologic examination within the first year of starting the medication. For those maintained on appropriate dosing and without major risk factors, annual screening beginning at 5 years of exposure is recommended.

REFERENCES:

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Philadelphia Dermatological Society
Children's Hospital of Philadelphia **April 16, 2021**

CASE: 15 **NOTE:** Right neck

AGE: 12 years **GENDER:** Female

PRESENTERS: Mohammed Dany M.D., Ph.D., Ziyang Xu Ph.D., and Michele Khurana, M.D.

HISTORY: Our patient presented with a 1-month history of a progressively enlarging erythematous rash on the right neck. She reported a long history of neck stiffness and intermittently used topical analgesics with partial relief. She denied any new constitutional symptoms (fevers, night sweats, weight loss) or other similar lesions. She did not recall any tick bite but noted walking her dog in a wooded area in Pennsylvania. An ultrasound of the area showed diffuse moderate soft tissue swelling and focal abnormality in the right sternocleidomastoid muscle. Lyme serologies were obtained, and she was started on oral doxycycline for empiric treatment. Despite treatment, the patient's rash continued to expand, and a punch biopsy of the lesion was performed.

MEDICATIONS: Lidocaine 4% cream PRN

PHYSICAL EXAMINATION: There is a non-tender, erythematous indurated plaque on the right lateral neck.

LABORATORY DATA:
Lyme ELISA, IgM and IgG normal

IMAGING DATA:
12/2/2020 Neck ultrasound: Moderate diffuse deep and subcutaneous soft tissue swelling, small focal abnormality in midportion of right SCM, possible tear, infection less likely, atypical for malignancy.

HISTOPATHOLOGY:
(12/15/2020, Right neck) The biopsy shows diffuse superficial and deep dermal infiltrates of large lymphoid cells with round nuclei, fine chromatin, indistinct nucleoli and scant cytoplasm. Focal small lymphoid aggregates are noted in the dermis. Immunohistochemical staining of the slides showed the neoplastic cells were positive for CD45, CD19, CD79a, Bcl-6 (strong), Bcl-2(dim), and had a high Ki-67 proliferative index. The findings were most consistent with infiltrative cutaneous non-Hodgkin B-cell lymphoma.

CASE: 15

DIAGNOSIS: Secondary cutaneous diffuse large B cell lymphoma (DLBCL)

DISCUSSION:

Our patient underwent a PET-CT showing diffuse infiltration of hypermetabolic malignant cells in the neck, right supraclavicular and axillary region, as well as the mediastinum, involving both muscles and pleura. An excisional biopsy of the cutaneous plaque and the draining lymph node showed DLBCL. Bone marrow biopsy was unremarkable. The final diagnosis was DLBCL, stage III. She is currently followed by oncology and recently completed 4 cycles of chemotherapy, re-staging pending.

DLBCL is the most common type of aggressive non-Hodgkin lymphoma (NHL) in the US, accounting for approximately 25% of new NHL diagnoses. While the average age of diagnosis is 60-65 years, DLBCL can also affect children, accounting for 10% of pediatric NHL. DLBCL may arise from both lymph nodes or extra-nodal sites, such as the GI tract, brain, testes, thyroid, breast, bone, and skin in 40% of cases. Patients may present with rapidly progressive lymphadenopathy, constitutional symptoms, or site-specific symptoms for extra-nodal DLBCL.

There are two forms of cutaneous DLBCL. Primary cutaneous large B-cell lymphoma, leg type (PCDLBCL-LT), is a primary extra-nodal form of DLBCL. PCDLBCL-LT frequently presents on the leg in older patients 70-82 years of age. Secondary cutaneous DLBCL (SC-DLBCL) is a form of nodal DLBCL that has secondary cutaneous dissemination. SC-DLBCL typically presents on the legs as multi-focal cutaneous nodules, although occasionally as papules or plaques as seen in our patient. Age, baseline performance status, constitutional symptoms, extra-nodal and bone marrow involvement, and serum LDH levels are prognostic factors for DLBCL.

For SC-DLBCL, secondary cutaneous involvement suggests the patient is at a high risk of disease progression, and the interval between the initial diagnosis and the development of skin lesions is the most important prognostic factor. Treatment outcomes in children with DLBCL are generally favorable. Overall, our case highlights the importance of maintaining a high index of suspicion for an acute, rapidly progressing indurated rash in the pediatric population, as prompt tissue biopsy will allow for early diagnosis and timely treatment for a malignant process, such as DLBCL.

REFERENCES:

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Sehn LH, and Salles G. Diffuse Large B-Cell Lymphoma. New England Journal of Medicine 384:842-858, 2021.

Philadelphia Dermatological Society
Children's Hospital of Philadelphia **April 16, 2021**

CASE: 16 **NOTE:** Toenails

AGE: 5 years **GENDER:** Female

PRESENTERS: Daniel J. Lewis M.D., Adam I. Rubin M.D., and Albert C. Yan M.D.

HISTORY: Our patient is a 5-year-old girl who presents with a two-year history of laterally deviated, cracked great toenails. Her mother believes that these changes started two years ago but began to involve the base of the nails in the last month. No other nails have been affected. The patient says her nail changes are asymptomatic. Her mother states the cracking is worsened by swimming and running in shoes. They deny any known trauma to the areas, although her mother reports the patient exhibited gross motor delay as a young child and used to curl her toes. The patient was diagnosed with hand, foot, and mouth disease about 1.5 years prior to the onset of the nail changes. She had been evaluated by her pediatrician and a pediatric podiatrist, who prescribed clotrimazole daily for one month covered by socks, resulting in minimal improvement.

MEDICATIONS: Urea cream

PHYSICAL EXAMINATION: On the halluces, the longitudinal axis of the nail plate is deviated laterally. There is approximately 1-2 mm of intact nail plate followed distally by discontinuous nail dystrophy. There is minimal periungal erythema.

LABORATORY DATA: None

IMAGING DATA: None

HISTOPATHOLOGY:
(02/10/2021, Great toenails) The nail clippings show compacted keratin consistent with nail plate. A Periodic acid–Schiff stain is negative for fungal organisms.

CASE: 16

DIAGNOSIS: Congenital malalignment of the great toenails

DISCUSSION:

Congenital malalignment of the great toenails is a dystrophic disorder characterized by lateral deviation of the nail plates with respect to the longitudinal axis of the distal phalanx. It is thought to be due to an abnormality in the ligament connecting the matrix to the periosteum of the distal hallux. Findings are often present at birth but can also develop in infancy or childhood; however, the condition is usually asymptomatic until the child begins crawling, walking, or wearing shoes. The disorder also manifests as nail plate thickening and transverse ridging ("Beau's lines"), and discoloration can occur due to subungual hematomas or recurrent infections from repeated nail trauma. It is also the most common cause of onychocryptosis in children and adolescents, and it can also lead to onychomadesis. The characteristic findings can be unilateral or bilateral, but medial deviation or involvement of other digits is rare.

Treatment is largely guided by symptoms and the degree of deviation. Conservative management is recommended initially since the nail findings resolve spontaneously in 50% of patients, typically before age 10, including in those with severe symptoms. Therapeutic options include phenolization of the lateral matrix, which does not address the underlying malalignment but can reduce the painful proximal nail plate and decrease the risk of onychocryptosis. Surgery can be performed in individuals with severe symptoms, although the nail can only be rotated a maximum of 45 degrees.

REFERENCES:

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Philadelphia Dermatological Society
Children's Hospital of Philadelphia **April 16, 2021**

CASE: 17 **NOTE:** Scalp

AGE: 14 years **GENDER:** Male

PRESENTERS: Heather Milbar M.D., M.P.H. and Leslie Castelo-Soccio M.D., Ph.D.

HISTORY: Our patient presents for hair loss, which had worsened significantly in the months prior to presentation. He has a history notable for growth hormone deficiency since infancy, for which he has received growth hormone replacement since 18 months. His family history is notable for male pattern hair loss in patient's father (in his 30s) and patient's maternal grandfather (in his 20s). His hair loss became noticeable to the patient and his parents in October 2019, while he was receiving treatment with anastrozole. The hair loss was characterized as thinning at the temples and parietal scalp. Notably, his treatment with anastrozole began in August 2018. This medication was discontinued in December 2019, and the patient began treatment with topical minoxidil and a laser cap. Due to concerns that the patient's hair loss was progressing, he was subsequently started on finasteride.

MEDICATIONS: Anastrozole, somatropin

PHYSICAL EXAMINATION: Bilateral temples with reduced hair density and miniaturized hairs. Decreased hair density also noted on the sides of the scalp. No changes at crown of scalp and a baseline high hairline (stable from previous photographs). Normal eyebrows, eyelashes, and facial hair. The patient waxes leg hair because it is very dense.

LABORATORY DATA:
BMP, normal
Vit D, normal
TSH and Free T4, normal
FSH, LH, prolactin, normal
Testosterone and estradiol, normal
IGF, normal

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 17

DIAGNOSIS: Aromatase inhibitor-induced androgenetic alopecia, also known as endocrine therapy-induced alopecia (EIA)

DISCUSSION:

Aromatase inhibitor-induced androgenetic alopecia was initially reported in patients receiving endocrine therapy for hormone-receptor-positive breast cancer. Aromatase inhibitors, such as anastrozole, letrozole, and exemestane, block the conversion of androgens to estrogens, thereby suppressing estrogen production by 97-99%. Although the precise mechanism of aromatase inhibitor-induced androgenetic alopecia is unknown, it is hypothesized that increased tissue and serum levels of dihydrotestosterone contributes to the development of alopecia in susceptible patients. Effectively, aromatase inhibitors have the opposite effect as 5α-reductase inhibitors, such as finasteride.

While frequently seen in the adult population, androgenetic alopecia (AGA) in children is uncommon. When diagnosed in the pediatric population, a strong family history of AGA is often noted. EIA in the pediatric population was first report by Perper *et al.* in two adolescents treated for idiopathic short stature. Both patients developed a pattern of hair loss consistent with AGA within one year of starting an aromatase inhibitor. Of note, aromatase inhibitors are primarily used off-label in pediatrics for the treatment of endocrine disorders, including hyperestrogenism, hyperandrogenism, pubertal gynecomastia, short stature and delayed puberty.

Our patient was prescribed anastrozole to treat short stature secondary to growth hormone deficiency. He has a family history of AGA in both his father and maternal grandfather and was treated for over one year. Thus, we theorize that that our patient's treatment with anastrozole accelerated the development of AGA. There is limited data on treatments for EIA in adults, let alone in children. Perper *et al.* report using topical minoxidil and low-level laser therapy for their patients, though they do not describe the efficacy of these interventions. In our patient, we stopped treatment with anastrozole and initiated topical minoxidil and low-level laser therapy. Due to lack of significant hair regrowth, he was recently started on oral finasteride.

REFERENCES:

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Perper M, Herskovitz I, Tosti A. Aromatase inhibitor-induced hair loss in two adolescents. Pediatr Dermatol. 37:1125, 2020.

Philadelphia Dermatological Society
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CASE: 18 **NOTE:** Scalp, left upper eyelid

AGE: 30 months **GENDER:** Female

PRESENTERS: Olaf Rodriguez M.D., Albert Yan M.D., and Leslie Castelo-Soccio M.D., Ph.D.

HISTORY: Our patient presented at 25 days of life for evaluation of a large area of alopecia on the scalp that was present from birth. The patient was born at 40 weeks via uncomplicated vaginal delivery with no known past medical history. The alopecic area is slightly elevated and demonstrates decreased hair density. It has become more erythematous, but otherwise remains unchanged since birth and does not change with crying. The patient was also noted to have yellow-white papules on the left upper eyelid which were treated by a local ophthalmologist with topical erythromycin with no significant improvement. She is currently undergoing serial excisions of the alopecic fatty tissue on the scalp with plastic surgery.

MEDICATIONS: None

PHYSICAL EXAMINATION: Left vertex scalp with an area of relative alopecia and overlying telangiectatic skin change. The underlying bony table is intact on palpation. Left upper eyelid with yellow-white papules, extending onto the conjunctiva.

LABORATORY DATA:
Genetic testing (NevusGene Set [Washington University]), nonsynonymous missense somatic variant p.N546D noted within the FGFR1.

IMAGING DATA:
(09/06/18, US echoencephalography/head) Prominent thickening of the scalp subcutaneous fat underlying the area of abnormality at the left vertex region. No sonographic evidence of a discrete solid, cystic or vascular scalp mass, the skull immediately underlying the lesion appears intact.
(11/12/18, Brain, cervical, thoracic, and lumbar spine MRI, without contrast)
BRAIN: Diffuse prominence of the subcutaneous fat with more focal prominence at the left parietal vertex. Otherwise unremarkable noncontrast brain MRI.
SPINE: Intradural spinal lipoma extending from T1-T8 with mild anterior displacement and distortion of the spinal cord. Additional smaller lipomas at C2 and T8-10.

HISTOPATHOLOGY:
(11/12/18, scalp) The biopsy shows skin with minimal change.

CASE: 18

DIAGNOSIS: Encephalocranialcutaneous lipomatosis

DISCUSSION:

Encephalocranialcutaneous lipomatosis (ECCL) is a sporadic neurocutaneous disorder characterized by ocular, cutaneous, and central nervous system (CNS) anomalies. ECCL is hypothesized to be due to a post-zygotic, mosaic mutation. Fewer than 60 cases have been reported in the medical literature. As demonstrated in our patient, the most characteristic skin anomaly is nevus psiloliparus, a well-demarcated, alopecic fatty tissue nevus on the scalp, seen in 80% of affected individuals. Additional dermatologic features reported include frontotemporal or zygomatic subcutaneous fatty lipomas, nonscarring alopecia, focal dermal hypoplasia or aplasia of the scalp, periocular skin tags, and pigmentary abnormalities in a blaschkoid distribution. Key extracutaneous features include benign ocular tumors, most commonly choristomas of the eye (epibulbar dermoids or lipodermoids), and central nervous system lipomas (seen in 61% of patients). Seizures and intellectual disability are common, but one-third of affected individuals have normal intellect.

Laboratory test results are typically within the reference range, and there are no effective treatment modalities. The ocular and CNS anomalies are assessed with MRI, although the optimal monitoring interval remains unclear. The prognosis appears to correlate with the progression of neurologic lesions and intracerebral malformations. As in our patient, serial excisions of the nevus psiloliparus can be considered for cosmesis.

The molecular etiology of ECCL remains unknown. ECCL demonstrates phenotypic overlap with several other disorders associated with mutations in the RAS-MAPK and PI3K-AKT pathways. Exome sequencing from five unrelated individuals with ECCL identified two mosaic mutations within the tyrosine kinase domain of FGFR1 (N546K and K656E); these two residues are the most commonly mutated residues in FGFR1 and are associated primarily with CNS tumors. Our patient similarly demonstrated a nonsynonymous missense somatic variant p.N546D noted within the FGFR1. While classified as being of uncertain significance, as noted above, another missense variant noted at this position has previously been reported as pathogenic in association with ECCL. Furthermore, computational algorithms reportedly predict that p.N546D would cause deleterious changes in protein function within FGFR1, suggesting that these findings are consistent with ECCL in our patient.

REFERENCES:

Bennett JT, Tan TY, Alcantara D, et al. Mosaic activating mutations in FGFR1 cause encephalocraniocutaneous lipomatosis. Am J Hum Genet. 98(3):579, 2016.

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Philadelphia Dermatological Society
Children's Hospital of Philadelphia **April 16, 2021**

CASE: 19

NOTE: Scalp, face, trunk, extremities, buttocks, lips, tongue, vulva

AGE: 7 years

GENDER: Female

PRESENTERS: Claire Hannah M.D., Mary Larijani M.D., and Melinda Jen M.D.

HISTORY: Our patient presented with 18 months of a pruritic, blistering rash. The rash started as pruritic papules on the legs, and subsequently progressed to diffuse blisters and erosions involving the upper extremities, trunk, face, scalp, lips, tongue, and vulva. The patient did not respond to topical corticosteroids or oral antibiotics for presumed atopic dermatitis with bacterial superinfection. Based on clinical findings alone, she was initially diagnosed with linear IgA bullous dermatosis and started on oral erythromycin and prednisolone. Her symptoms improved on this regimen but recurred as prednisolone was tapered. Further workup with skin biopsy and laboratory testing was consistent with a diagnosis of epidermolysis bullosa acquisita (EBA). She was started on oral dapsone and continued on prednisolone. Despite treatment, she experienced recurrent flares and remained steroid-dependent, so rituximab was added to her treatment regimen. Two months after completing 2 infusions of rituximab 750mg/m2 given 2 weeks apart, her symptoms as well as clinical findings have improved. She remains on dapsone 2 mg/kg/day and prednisolone.

MEDICATIONS: Triamcinolone ointment, prednisolone, dapsone, rituximab

PHYSICAL EXAMINATION: The patient has scattered erythematous papules and thin plaques with numerous erosions, crusting, and rare intact vesicles on the scalp, face, trunk, extremities, buttocks, and groin. She also has erosions involving the mucosal lips and tongue.

LABORATORY DATA:
ELISA: positive for anti-collagen VII antibodies. Negative for antibodies against BP180 or BP230.
Indirect immunofluorescence (IIF): linear deposits of IgG4 on the dermal side of salt-split skin.
ANA: undetectable.

IMAGING DATA: None

HISTOPATHOLOGY:
(11/5/20, posterior neck) The biopsy shows a subepidermal blister with neutrophils and eosinophils. Direct immunofluorescence (DIF) shows linear deposition of IgG, IgM, and C3 at the basement membrane zone.

CASE: 19

DIAGNOSIS: Epidermolysis bullosa acquisita

DISCUSSION:

Epidermolysis bullosa acquisita (EBA) is an acquired mucocutaneous bullous dermatosis mediated by autoantibodies directed against collagen VII, a major component of the anchoring fibrils of the dermal-epidermal junction (DEJ). It classically presents as a mechanobullous disorder characterized by skin fragility and noninflammatory, trauma-induced bullae that heal with milia, dyspigmentation, and scarring. Inflammatory and mixed inflammatory-mechanobullous subtypes also exist. EBA rarely presents in childhood. Children typically present with inflammatory EBA, which can mimic other subepidermal bullous diseases, leading to a delay in diagnosis and treatment. Mucosal involvement is common in pediatric EBA and can result in significant morbidity if not recognized early. Unlike EBA in adults, pediatric EBA is not typically associated with underlying systemic conditions such as malignancy or autoimmune disease.

Because pediatric EBA can present similarly to numerous other hereditary and acquired mucocutaneous bullous dermatoses, tissue biopsy is necessary for definitive diagnosis. Classic EBA demonstrates a subepidermal blister with linear deposition of IgG and complement at the DEJ on DIF. IIF demonstrates antibody binding to the dermal side of salt-split skin. Serologic detection of IgG antibodies against collagen VII by ELISA further supports a diagnosis of EBA. Serum concentrations of anti-collagen VII antibodies are correlated with disease activity and can be utilized as a marker for treatment response.

Compared to adults with EBA, children tend to respond more rapidly to treatment, with an average treatment duration of 3 years. Combination therapy with oral corticosteroids and dapsone is the mainstay of treatment. Patients with refractory disease can be challenging to treat and require more aggressive therapies such as other immunosuppressants, rituximab, IVIG, and plasmapheresis. Rituximab, either as monotherapy or in combination with other agents, has been shown to induce long-term remission in cases of refractory EBA. When combined with IVIG, rituximab may also provide utility in terminating acute disease.

REFERENCES:

Delago L, Aoki V, Santi C, et al. Clinical and immunopathological evaluation of epidermolysis bullosa acquisita. Clin Exp Dermatol. 36(1):12, 2011.

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Philadelphia Dermatological Society
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CASE: 20 **NOTE:** Hands, feet

AGE: 5 years **GENDER:** Female

PRESENTERS: Olaf Rodriguez M.D. and Albert Yan M.D.

HISTORY: Our patient presented at 3 years of age with a 3 month history of fluid-filled lesions and fissures of the bilateral palmar and plantar surfaces. Previous wound cultures were positive for MRSA, and the patient received multiple courses of antibiotics upon development of lesions with minimal improvement. The patient notes pruritus of palms and pain on plantar surfaces with ambulation. The patient's father has a history of palmoplantar keratoderma. Prenatal genetic testing did not reveal any mutations associated with palmoplantar keratoderma, and there is no history of deafness in the family. Topical treatment with urea 20% cream, tretinoin 0.025% cream, and mupirocin 2% ointment was initiated with clinical improvement; however, due to irritation, topicals were discontinued. With liberal use of emollients, the patient has experienced reduction in lesion thickness.

MEDICATIONS: Amoxicillin/clavulanic acid, sulfamethoxazole-trimethoprim, cephalexin, urea 20% cream, tretinoin 0.025% cream, mupirocin 2% ointment

PHYSICAL EXAMINATION: On exam, there is thin hyperkeratosis of the palmar aspect of patient's bilateral hands, sharply demarcated at the wrist flexures. Similar findings are observed on soles of feet and plantar aspects of the toes. Mild interdigital scaling and erythema of the toes is noted. No nail abnormalities present.

LABORATORY DATA:
KRT9 Gene testing: Heterozygous for both a pathogenic variant and a variant of uncertain significance in the KRT9 gene. The presence of the R163Q pathogenic variant is consistent with the diagnosis of epidermolytic palmoplantar keratoderma. This analysis cannot determine whether these variants are on the same (*in cis*) or different (*in trans*) alleles. The significance of the presence of the L149R variant in this individual is uncertain.

IMAGING DATA: None

HISTOPATHOLOGY: None

CASE: 20

DIAGNOSIS: Epidermolytic palmoplantar keratoderma

DISCUSSION:

Epidermolytic palmoplantar keratoderma (EPPK) is a type of diffuse palmoplantar keratoderma that typically becomes apparent at birth/early childhood characterized by diffuse, compact, hyperkeratosis limited to the palms and soles. The lesions respect a sharp demarcation at the volar border, but may demonstrate a surrounding erythematous margin. Hyperhidrosis is a frequent associated symptom. The mode of inheritance of EPPK is autosomal dominant (although de novo mutations have been reported), caused by a heterozygous mutation in the keratin genes KRT1 or KRT9. These mutations disrupt the formation of keratin intermediate filaments, leading to physical weakness of the cytoskeleton, and resulting in epidermolysis microscopically, which can be appreciated as fluid-filled lesions clinically. KRT9 is only expressed in the keratinocytes of the palms and soles, lending to the unique distribution observed in EPPK (as compared to global skin involvement seen with KRT1 mutations). On histology, hyperkeratosis with vacuolar degeneration of cells in the granular and spinous layers of the epidermis is characteristic.

Although treatment of hereditary PPK is difficult, primary goals should focus on reducing/softening hyperkeratotic skin and controlling discomfort at involved areas. Gentle mechanical removal of scale, such as with a pumice stone, following soaking of involved areas, along with liberal use of emollients, may help reduce lesion thickness. Some patients benefit from physical therapy if contractures of the palms evolve. Management of secondary bacterial/fungal infections is also crucial, and may be suspected if involved areas develop worsening pain, maceration, and/or odor, and should be treated appropriately with topical or systemic antimicrobial therapy. Additionally, topical keratolytics containing urea, lactic acid, salicylic acid, or propylene glycol can be used to soften the hyperkeratotic lesions. Topical retinoids may be utilized when irritation from these agents is not excessive. Systemic retinoids have been utilized in some cases, and improvement with surgical treatment is also described in a handful of reports.

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Philadelphia Dermatological Society
Children's Hospital of Philadelphia **April 16, 2021**

CASE: 21 **NOTE:** Left upper extremity

AGE: 8 years **GENDER:** Male

PRESENTERS: Christina Del Guzzo M.D., Diego Dasilva M.D., Mary Larijani M.D., Ilka Arun Netravali M.D, Ph.D., Michele Khurana M.D., Denise Adams M.D., and James Treat M.D.

HISTORY: Our patient was noted to have swelling and bluish discoloration of the left hand at birth that gradually spread proximally to involve the entire left upper extremity and chest wall. He was diagnosed with kaposiform lymphangiomatosis and found to have lymphatic disease in his bone and spleen. The involved area is painful and has been complicated by cellulitis and bacteremia. He was initially treated with sirolimus but continued to have exacerbations associated with fevers, thrombocytopenia, and painful swelling of his lymphatic malformation. A biopsy was performed revealing a PIK3CA mutation and the patient was started on alpelisib, a PI3K inhibitor, in February 2020. He has shown significant improvement with less swelling, no episodes of cellulitis, and stable blood counts.

MEDICATIONS: Alpelisib, gabapentin

PHYSICAL EXAMINATION: There is swelling of the entire left upper extremity with subtle violaceous discoloration of the digits and a foreshortened right fourth digit without ulceration.

LABORATORY DATA:
WBC, normal
Hemoglobin, 10 (11.5-15.5)
Hematocrit, 30.2 (35-45%)
Platelet count, 108 (150-400)
D-dimer, 5.927 (0-0.499)
Fibrinogen, normal
LFTs within normal limits
Genetic tissue analysis, PIK3CA mutation

IMAGING DATA:
(2/11/2021, MRI Whole Body) Stable pattern of lymphangiomatosis with dominant involvement of the left axillary region and left upper extremity. Scattered areas of bone signal abnormality. Cystic changes in the spleen.

HISTOPATHOLOGY: None

CASE: 21

DIAGNOSIS: Kaposiform lymphangiomatosis with PIK3CA mutation on alpelisib

DISCUSSION:

Vascular anomalies are characterized by the abnormal development of blood and/or lymphatic vessels and may be associated with a range of other anomalies, including segmental overgrowth as well as abnormalities in the musculoskeletal, cutaneous and neurologic systems. They can cause a variety of clinical problems such as disfigurement, pain, coagulopathy, bleeding, and end organ dysfunction. Historically classified as separate entities, diseases such as CLOVES (Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Scoliosis/Skeletal and Spinal), FAO (Fibroadipose hyperplasia or Overgrowth), KTS (Klippel-Trenaunay Syndrome), and megalencephaly-Capillary Malformation syndromes are now considered under the spectrum of PIK3CA (phosphatidylinositol-3-kinase/AKT/mTOR)-Related Overgrowth Syndromes (PROS). PROS encompasses a broad phenotypic spectrum of syndromes associated with vascular malformations and overgrowth caused by somatic activating mutations in the *PIK3CA* gene; these mutations lead to overactivation of the PI3K/AKT/mTOR pathway that plays a critical role in cellular proliferation, survival advantage, and angiogenesis.

Kaposiform lymphangiomatosis is an aggressive lymphatic anomaly. It is associated with serious complications including pleural/pericardial effusions, consumptive coagulatopathy, ascites, and bone destruction. Histologically, it is characterized by abnormal lymphangiogenesis, thin-walled lymphatic channels with flattened endothelial cells, and focal areas of spindled endothelial cells. Imaging and biopsy are often necessary for diagnosis, and elevated blood levels of angiogenic factors, such as angiopoietin and VEGF, have been reported.

The recent paradigm shift toward molecular classification of vascular anomalies has allowed for the development of targeted therapies. Sirolimus is a specific inhibitor of mTOR, a serine/threonine kinase in the PI3K/AKT pathway, and has shown efficacy in PROS with diminished symptoms and improvement in disease severity. More recently, alpelisib, an oral PI3K inhibitor that is FDA-approved for hematologic malignancies and breast cancer, has shown notable improvement in malformations within the PIK3CA spectrum including vascular anomalies.

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