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The Adaptability of the Bilobed Transposition Flap
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Dear Readers,

Our journal has a proud history of scholarship and volunteerism. It has been a steady platform for us to publish our interesting cases and share ideas. Traditionally, the annual-paper residency requirements have made up the bulk of our submissions. As you probably realize, that requirement is going away. This leaves the journal without an immediately identifiable pool of potential material. Submissions from sources outside this requirement are currently too anemic to populate a journal. So we find ourselves at a crossroads with our endeavor.

The near future may see a day when the journal ceases to exist. I have spoken with many of you, and the general sentiment is that we are duplicating efforts already covered by other journals. This is a valid point. But many of you also enjoy the journal and want to see it survive. Personally, I am tremendously enriched by reviewing the articles, as it keeps me current with literature I would otherwise never read. We are lucky to have a panel of talented and dedicated reviewers in place who volunteer their time and energy for the journal. Additionally, our infrastructure and finances are in place to continue operations for quite some time. If we continue to receive quality articles from you, there is no reason we cannot continue to publish.

The coming months will determine the journal's fate. I want to stress this point: There is a very real possibility our beloved journal will end. If it is valuable to you, let us know by reading it online, utilizing the CME offered, and/or submitting an article. Ultimately, our journal cannot exist without your submissions. If you deem it has no value, your silence will be a deafening call to stop the press.

“To be or not to be: that is the question.”

You have our ear.

Respectfully,
Derrick
Hello, Everyone,

It’s hard to believe summer is here. Thank you to everyone who participated in our spring conference at the Ritz Carlton in Atlanta.

On Thursday, March 30, 2017, our annual election was held, and Dr. Alpesh Desai handed the presidential gavel to Dr. Karthik Krishnamurthy. Click here to view the 2017–2018 AOCD officer lineup.

Just a reminder that we now offer Category 1B CME credit for reading the JAOCD. Also, after our 2017 Fall Meeting, which will take place from October 24–28, 2017, at the Intercontinental New Orleans, the AOCD will begin partnering with the Association of Osteopathic State Executive Directors (AOSED) to offer online, on-demand Category 1A CME. Look for more information in our weekly Thursday Bulletin.

We are planning several surprises for our Fall Meeting in New Orleans, so you won’t want to miss it.

Speaking of fun and festivities, grab your calendars now and mark off March 19-25, 2018, for the 2018 Spring Meeting at the Hilton West Palm Beach. The year 2018 will be the AOCD’s 60th anniversary, and plans are already underway for a grand celebration. This will be the first time the AOCD offers the State of Florida re-licensure requirements courses, planned for Sunday, March 25, 2018.

In our brochures, you may have noticed the lengthy disclosures regarding our CME activities and speakers. This notification is a requirement of the AOA and the ACCME. We continue to closely monitor potential conflicts of interest to avoid any commercial bias during our CME activities. A conflict of interest exists when an individual has an opportunity to affect CME content about products or services of a commercial interest with which he or she has a financial relationship. The AOCD’s decisions regarding CME activities are made free of the control of any commercial interest, and all decisions on the disposition and disbursement of commercial support are made by the AOCD. If you are interested in learning more about the Standards for Commercial Support, click here.

Save The Dates!
2018 Spring Meeting: March 19-25, 2018, at the Hilton West Palm Beach, 600 Okeechobee Blvd., West Palm Beach, FL
2018 Fall Meeting: October 9-13, 2018, at the Westin San Diego, Gaslamp Quarter, 400 West Broadway, San Diego, CA

Thank you for your continued support of the AOCD. Please call (800-449-2623) or email (dermatology@aocd.org) the AOCD office if you need assistance.

Thank you,

Marsha Wise
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Abstract

The bilobed transposition flap began as a technique to repair the nasal tip. The purpose of our review is to catalogue the successes of the bilobed flap since it was first described by Esser in 1918, as well as the modifications created by other physicians since then. A PubMed Search from 1900 to 2015 for the words “bilobed flap” yielded 150 results. In the 35 cases described, there were new developments in the design and use of the bilobed flap. Varying the angle of rotation, length, and width of the flaps allowed for variability to meet the demands of different anatomical locations. Each of the cases demonstrated the benefits of the bilobed flap technique in allowing for ample blood supply, proper healing, and preservation of anatomy. The functional and aesthetic results achieved further validate the use of the bilobed flap in locations other than the nasal tip.

Introduction

The bilobed flap was first described in German literature in 1918 by Dr. Johannes Esser as a two-pedicled flap. All later variations maintain the same general principle of utilizing a double transposition in areas where a single transposition flap is not adequate. Bilobed flaps are used in reconstructive surgeries that require both recruitment of skin from a site with more tissue laxity and a low-tension closure to improve healing and scar aesthetics. When designing a bilobed flap, it is crucial to the survival of the flap to maintain an adequate blood supply with a sufficient pedicle. What makes the bilobed flap highly useful is its ability to utilize a common pedicle to move skin from an area of further distance and greater laxity to the site of a defect with limited mobility. This strategy is similar to that of the rhombic transposition flap with a Z-plasty, but transposes a greater area of skin while maintaining the mobility. Also, by rotating the flap only 90°, the bilobed flap minimizes the problem of inadequate blood flow to the tips of the margin that is present in other techniques, such as those that require 180° rotations. In addition, the local transposition of skin in this flap creates a closer skin match than do alternatives like skin grafts. Other variations of the bilobed flap design have changed lobe sizes and rotation angles to accommodate varied defects and body locations.

Methods

A PubMed search from 1900 to 2015 for the words “bilobed flap” yielded 150 results. Of those, only 35 papers were relevant and included sufficient information on the bilobed flap or proposed modifications. The other 115 papers either did not fit into the scope of this paper or were not sufficiently descriptive. The 35 papers included in our research addressed cases involving anatomical sites including the nose (30), ear (13), forearm (13), hand (20), cheek (4), thorax (19), genitals (11), foot (6), eye (16), mouth (15), and leg (3).

Discussion

Nose

The nose can be difficult to repair due to the limited available sources from which to locally harvest tissue and the high potential for distortion. If planned properly and well executed, a bilobed flap can restore the natural appearance of the nose. When the flap is not...
precisely planned, undersizing can create contraction and distortion of the symmetry of the nose, and oversizing can cause pincushioning and depression.\(^7\)

Zitelli was the first to modify Esser’s bilobed flap.\(^6\) The original design indicated an angle of rotation of 90° for each lobe, for a total angle of 180°.\(^1,2\) In 1989, Zitelli proposed the most effective angle of rotation as 45° for each lobe, a modification that allowed for greater precision when reconstructing nasal defects.\(^6\)

Zitelli’s modification also makes the primary lobe the same size as the defect, but it makes the secondary lobe longer to avoid the formation of a dog ear upon primary closer of the secondary-lobe donor site. Zitelli’s use of smaller, 45° angles instead of 90° angles for each lobe was validated by Miller (Figure 1).\(^8\) In an experiment looking at three different bilobed flaps that varied in angle of flap rotation (30°, 45°, and 60°, respectively), Miller demonstrated that a 45° rotation maximizes benefits.\(^x\)

Xue suggested a modification to the Zitelli flap that reduces the risk of alar retraction (Figure 2).\(^9\) This modification changes the proportions of the lobes while maintaining Zitelli’s rotation angles. In Xue’s approach, the primary lobe is 10% longer than the length of the defect but retains the same width. The secondary lobe is 130% longer than the length of the defect, and the width is two-thirds the width of the primary lobe. This alteration avoids distortion created by tension, as explained by Dzubow’s principle of pivotal restraint, which says that a transposition flap will be tethered to the base of the flap, thus creating a tension vector that pulls upward on the alar rim.\(^16\)

Cheek
A benefit of the bilobed flap for lateral cheek reconstruction is that donor skin can be recruited from the inferior preauricular region, which is well matched for texture and color. White describes a bilobed flap on the cheek in which the lobe distal to the wound is made smaller than the proximal lobe, between 2:1 to 4:1 in length-to-width ratio (Figure 3).\(^11\)

Ear
When considering reconstruction of the auricle, there are two major modifications of the bilobed flap for repair of the earlobe — the Gavello and the D’Hooghe techniques.\(^12\) The Gavello technique utilizes a horizontal bilobed flap inferior and posterior to the defect (Figure 3). The D’Hooghe technique uses a lobe from each of the preauricular and postauricular areas to reconstruct the earlobe (Figure 4).\(^13\) The major disadvantage to the D’Hooghe technique is it can only be used for small defects.

Brent’s modification is used for large defects of the lower auricle — primarily the earlobe — and utilizes a cartilage graft to counteract the contraction of tissue during wound healing.\(^14\)

Gupta describes a bilobed variation similar to D’Hooghe’s (Figure 4). This modification uses a lobe from the preauricular area and a lobe from the postauricular area, which is comparable to the D’Hooghe technique; however, the base is smaller and positioned more superior to the sutured edges of the inferior margin of the lobe.\(^15\)

Weerda proposed another modification for repair of the helix and earlobe that also uses cartilage grafts to reconstruct the earlobe and helix. This flap is a variation of the Gavello bilobed flap, but it harvests costal cartilage to construct the inferior portion of the helix and prevent contraction of the earlobe.\(^16\)

Rodríguez suggested a method for repair of defects of moderately sized earlobes in which a bilobed flap has an anterior base, and the primary lobe is the same size as the defect. The secondary lobe is smaller and transposed on the posterior aspect of the earlobe.\(^17\) The disadvantage to this variation is scars below the earlobe.

Upper Extremities
Nikkhah describes using a bilobed flap for the excision of a sarcoma on the dorsum of the forearm.\(^18\) In this approach, the first flap is the same size as the defect, and the second lobe is twice as long as the first flap but half the width.

Zhang describes a flap for the thumb that includes skin from the second web of the hand and the dorsum of the index and middle fingers.\(^19\) The entire flap with a double neurovascular pedicle is elevated and mobilized. The skin is transferred...
Amputated fingers have been repaired using techniques described by Saba, known as a DMCA (dorsal metacarpal artery) flap.25 The first and second dorsal metacarpal arteries are used to resurface the phalangeal stumps. Saba uses an S-shaped incision to maintain the innervation and blood supply for the phalanges. The benefit of the modification is that it is a single stage procedure with high success rate.

Sahin uses the bilobed flap surgery to create web spaces in the syndactyly release.26 The base of the bilobed flap is designed on the dorsum of the hand, between the metacarpal heads of the involved fingers. The flap is rectangular, with a 2:1 length-to-width ratio. Markings are on the palmar side of the fingers, and the incisions are zigzag mirror-image triangular flaps. The triangular flaps are then wrapped around the newly synthesized fingers.

Vuillermin used a bilobed flap that improved hand position, soft-tissue releases, skeletal realignment, muscular rebalancing, and free skeletal transfer for radial dysplasia.27 The bilobed flap is unique in that it avoids the forearm stiffness and ulnar injury that can result from other surgical procedures.

Trunk
Bilobed flaps are used on the torso with burns in the axillary region. Smith created a modified bilobed flap to place scars in a relatively inconspicuous location (anterior and posterior axillary lines) with no breast torsion.28 The technique involved placing the flap laterally and decreasing the angle of rotation of each lobe from 90° to 45°. The point of rotation may be centered cephalic to the triangular space to include the anterior branches of the circumflex scapular artery.

Charanek describes a bilobed thoracoabdominal myocutaneous flap to cover large wounds secondary to radical mastectomies.29 The technique changed the angles from 60° to 90° to allow for larger coverage. Also, the flaps were modified caudally to diminish the tension and lower the rate of dehiscence and necrosis.

Figure 5. a) The skin lobes created from the dorsum of the index and middle fingers, labeled 1 and 2, distally at the level of the proximal interphalangeal (PIP) joints and proximally at the MCP joint. An S-shaped incision is made on the dorsum of the second metacarpal. Lobe 2 is transposed to cover below the first metacarpal. Lobe 1 then covers the amputated thumb. b) Lobes 1 and 2 are sutured into place. Lobe 3 represents the hand area that will be covered by a skin graft from the thigh. c) Lobe 3 skin grafted, and all incisions are sutured closed.

Lower Extremities
The versatility of the bilobed flap is further demonstrated at sites of the lower body (Figure 6). Sharkirov describes a technique in which ulcers on the plantar surface of the foot were closed using bilobed flaps.26 The angle between the lobes was the traditional 90° as described by Esser, but the size of the lobes was modified so the secondary lobe was smaller than the primary lobe, which is more characteristic of later modifications.

Genitalia
Grishkevich describes a medially based bilobed flap much larger than those previously discussed.27 The primary lobe is 20 cm long and 10 cm wide; the secondary lobe is shorter but maintains the 10 cm width. Grishkevich continues with the Esser design of a 180° total rotation to transpose skin from the inguinal region into a defect in the anogenital area. A second stage was completed several months later to remove dog ears.

Sampaio describes a bilobed repair for a circular, 6.8 cm defect following an HPV lesion excision in the pubic region.28 The flap employed the modern, 45° rotation of each lobe, for a total of 90° along the base; but while the primary lobe was the same size as the defect, the secondary lobe was longer and narrower. Lee described a similar bilobed flap technique for the treatment of sacral sores.29 Sharkirov describes a technique in which ulcers on the plantar surface of the foot were closed using bilobed flaps.26 The angle between the lobes was the traditional 90° as described by Esser, but the size of the lobes was modified so the secondary lobe was smaller than the primary lobe, which is more characteristic of later modifications.

Conclusion
Many authors have considered bilobed flaps ideal for aurral and nasal procedures; however, the use is much broader. Overall, the utility of the bilobed flap has expanded over the past century to areas other than the nasal tip. The design allows for various components to be changed to accommodate the requirements of a particular area of the body, such as rotation angle and size of the lobes.

Further design improvements and innovative uses appear to be in the future as the bilobed flap becomes more prevalent in the reconstructive surgical arena.
References


Acknowledgements

Figure 6 was provided by Michael Zaycosky, DO.
Burrow’s Graft for Nasal Tip Defects as an Alternative to More-complex Reconstructive Surgery Following Mohs Surgery: A Case Presentation and Discussion

Kevin Myers, DO,* Rand Colbert, MD**

*Dermatology Resident, PGY2, Silver Falls Dermatology, Salem, OR
**Dermatologist, Cedar Dermatology, Cedar City, UT

Abstract

Background: Following Mohs surgery, defects of the nasal tip are often repaired with complex flaps and grafts harvested from distant sites. Both of these options may result in increased complications or poor cosmetic outcomes compared to simpler options. Objective: Demonstrate the utility of the Burrow’s graft as an alternative to other reconstructive surgery options for defects of the nasal tip. Methods: We present two cases in which Burrow’s grafts were used to repair medium-to-large defects of the nasal tip. Results: Excellent cosmetic outcomes were achieved in both cases. Conclusion: The Burrow’s graft is a great reconstructive option for medium-to-large defects of the nasal tip. Furthermore, it is a simple technique with quick closure time, has a relatively low complication rate, and offers reduced cost to the patient compared to outside referral for defect closure.

Introduction

Because of its sun-exposed location and proliferative follicular constitution, the nasal tip is one of the areas of highest prevalence for non-melanoma skin cancers. Unfortunately, even a small defect on the nasal tip following micrographic surgery can be challenging to repair with a cosmetically acceptable result due to the limited elasticity of the sebaceous tissue, convex topography and lack of donor tissue at the site. Patients frequently undergo extensive, often multi-stage reconstructive surgeries to repair these defects. Such reconstructive efforts range from forehead flaps, dorsal nasal or bilobed flaps, and skin grafts harvested from distant sites to more-imaginative repairs. Due to a lack of time or skill on the dermatologist’s part, and reimbursement issues (multiple-procedure reduction), next-day reconstruction or referral to a plastic surgeon are often the preferred avenues for accomplishing the required repair. This exposes the patient to discomfort, infection risk, high cost, and inconvenience.

The outcomes of these efforts range from excellent to unacceptable. Large flaps from the forehead, nasal dorsum or nasal sidewall may produce a bulky contour or “pin-cushioning” that patients find cosmetically distressing. They also leave long scars because of the need to recruit the flap from the donor site. Hematomas and infection are more likely with flaps because of the additional incisions required and the need to extensively undermine at times. A graft from a distant site like the post-auricular or supraclavicular skin is even more likely to frustrate a patient because it results in a smooth, white “patch” that poorly matches the more sebaceous nasal skin. Other full-thickness grafts may poorly resemble the nasal skin in texture, actinic damage, and hair density. A standard vertical primary closure of the nasal tip produces acceptable results when the defect is small, but tends to flatten the tip in larger defects; it also tends to produce a wider scar on highly sebaceous noses than on less-sebaceous ones.

In dermatologic surgery, a wise paradigm to follow is to perform the least complex procedure that will result in the best possible outcome with the fewest attendant risks and adverse events. In other words, “Bigger isn’t always better,” and “Just because we can, doesn’t mean we should.” In our experience, one simple option for repairing defects of the nasal tip is a Burrow’s graft, which takes advantage of the relative laxity of the skin of the nasal bridge. For defects too large to perform a vertical primary closure, a single Burrow’s triangle may be excised from the skin superior to the defect and then used as a graft following closure of the Burrow’s triangle defect. We present two patients with sizable defects of the nasal tip repaired with Burrow’s grafts recruited from nasal-dorsum skin.

Case 1

A 68-year-old female underwent three stages of Mohs surgery for an infiltrative BCC of the nasal tip, resulting in a 1.6 cm x 2.2 cm defect with exposed cartilage at the base (Figure 1). After discussing repair options with the patient, a Burrow’s triangle was excised from the nasal dorsum immediately superior to the defect (Figure 2). The secondary defect created by removal of the Burrow’s triangle was closed with 6-0 polyglactin 910 (Vicryl®) sutures, thereby reducing the size of the primary defect by approximately 50%. After trimming the Burrow’s triangle (graft) slightly to conform to the shape of the defect, the graft was sutured to the defect with numerous interrupted 6-0 nylon sutures (Figure 3). The site was covered in petrolatum and a pressure bandage, and the patient was prescribed cephalexin 500 mg orally three times a day for 10 days. One week later, the sutures were removed, and three weeks later the site had nearly completely healed, with one small area of necrosis that was still granulating (Figure 4). Three months later, the surgery site was completely healed and nearly undetectable (Figure 5).

*Correspondence: Kevin Myers, DO; kmyers@silverfallsderm.net
other grafts, which, in our experience, typically to produce a nearly perfect cosmetic result, unlike actinic damage, and texture. This has the potential of the nose to the extent that primary closure reduction rarely compromises the overall anatomy effect reduces the size of the defect by half. That the donor-site closure secondarily reduces the size larger the harvested Burrow’s triangle, the more one major advantage of this technique is that the donor site (the nasal bridge), which allows for relatively quick closure compared to a bilobed, dorsal-nasal or forehead flap. There is ample skin laxity at the skin cancer removal, “punting” the patient to a facial plastic surgery colleague. repair for the defect on a subsequent day is often the most appealing course of action. For the patient, however, this only prolongs the experience and may add further anxiety due to unfamiliarity with the new physician, the need for anesthesia and inherent additional costs. While most dermatologists who perform Mohs surgery have the skill to perform more-complex flaps to repair nasal tip defects, the time required and additional risks incurred might not be worth the incrementally smaller reimbursement due to the multiple-procedure reduction rule. Furthermore, the variability in outcomes from larger flaps might dissuade a dermatologist from attempting a more “heroic” closure.

In our experience, the Burrow’s graft is an ideal option for treating medium-to-large nasal tip defects because it allows for relatively quick closure with consistently reproducible and excellent cosmetic results. One major advantage of the Burrow’s graft is that it requires little constructive planning compared to a bilobed, dorsal-nasal or forehead flap. There is ample skin laxity at the donor site (the nasal bridge), which allows for large grafts to be harvested without making closure of the donor site difficult. To the contrary, one major advantage of this technique is that the larger the harvested Burrow’s triangle, the more the donor-site closure secondarily reduces the size of the Mohs defect. In many cases, this beneficial effect reduces the size of the defect by half. That reduction rarely compromises the overall anatomy of the nose to the extent that primary closure might (e.g., flattening of the nasal tip). This reduction in defect size significantly simplifies closure when compared to larger flaps that tend to create multiple secondary defects and longer scars without necessarily diminishing the defect size. Unlike grafts harvested from distant sites, Burrow’s grafts taken from the nasal bridge closely match the original nasal tip skin in color, sebaceous density, actinic damage, and texture. This has the potential to produce a nearly perfect cosmetic result, unlike other grafts, which, in our experience, typically produce very poor cosmetic matches.

Discussion
The Burrow’s graft is a simple, perhaps underutilized repair technique that takes advantage of the skin adjacent to the defect site, where a Burrow’s triangle might otherwise be removed for another repair option. Mohs surgery on the nasal tip can be anxiety-provoking for both the patient and the dermatologist, especially if multiple stages are required to remove the tumor and if the resultant defect is larger than 1 cm. In such a circumstance, when the patient has spent several hours in the dermatologist’s office or surgical suite, and the closure of the defect looms as an even bigger challenge than the skin cancer removal, “punting” the patient to a facial plastic surgery colleague. for repair of the defect on a subsequent day is often the most appealing course of action. For the patient, however, this only prolongs the experience and may add further anxiety due to unfamiliarity with the new physician, the need for anesthesia and inherent additional costs. While most dermatologists who perform Mohs surgery have the skill to perform more-complex flaps to repair nasal tip defects, the time required and additional risks incurred might not be worth the incrementally smaller reimbursement due to the multiple-procedure reduction rule. Furthermore, the variability in outcomes from larger flaps might dissuade a dermatologist from attempting a more “heroic” closure.

The conventional wisdom in surgical dermatology regarding skin grafts is that meticulous graft preparation, graft thinning, soaking in saline, and bolster placement over the graft all improve graft survival and ultimately surgical outcomes. From the dozens of Burrow’s grafts we have performed in our clinic, we have not seen a clear correlation between these tenets of “graft dogma” and real life outcomes. Anecdotally, even for undersized grafts that require more suturing or stretching and for grafts placed over cartilage (as in Case 1), we haven’t appreciated a significant difference in final cosmetic result compared to cases of optimal graft placement. It may be that because of the dense proliferative follicular composition, the rich vascularity or the optimal “tissue-match” of the graft to the recipient site, there are simply better cosmetic outcomes. In fact, we have noticed that despite a high percentage of these grafts experiencing a superficial graft necrosis, in the majority of cases the result is very good to excellent. Even with full-thickness graft necrosis, the cosmetic outcome is usually very good. In any instance of graft necrosis, the patient should be instructed to leave the eschar in place, and keep the entire site moisturized with a thick layer of petrolatum. Oral antibiotics may assist in healing and partial graft survival.

As with all techniques, cosmetic outcomes with the Burrow’s graft can occasionally be less than acceptable. Most of these result from full-thickness graft necrosis, leaving the final scar either thin and papyery overlying the cartilage, or depressed, with a defined border at the juncture with the normal nasal skin. Dermabrasion or laser resurfacing can improve both of these unwanted effects. In extreme cases, the scar can be excised and another closure attempted. Because of the reduction in defect size prior to graft placement when the Burrow’s defect is closed, excising a scar from a Burrow’s graft leaves a much smaller defect than the original Mohs defect. In all cases, the physician should wait at least six months before attempting any corrective measure.

Conclusion
Nasal tip defects following Mohs surgery can be a daunting problem for dermatologists given the time constraints of a busy practice and the inherent complexity of the common repairs for these defects. With physician and patient anxiety factored into the situation, it is sometimes easiest (but often not best for the patient) to simply refer to a facial plastic surgeon for repair on a subsequent day. As demonstrated by these two cases, the Burrow’s graft can be a time-efficient, relatively simple alternative to more-complex repair options. Because of these factors, and because of the consistently excellent cosmetic outcomes, the Burrow’s graft should be considered whenever a medium or large nasal tip defect results from Mohs surgery.
References


Agiolymphoid Hyperplasia with Eosinophilia on the Lower Extremity: Case Report with Brief Review

Summer Moon, DO,* Katherine Braunlich, DO,** Howard Lipkin, DO,** Annette LaCasse, DO***

*Dermatologist Resident, PGY4, Beaumont Farmington Hills Dermatology, Farmington Hills, MI
**Traditional Rotating Intern, PGY1, Largo Medical Center, Largo, Florida
***Dermatologist, Beaumont Farmington Hills Dermatology, Farmington Hills, MI

Disclosures: None
Correspondence: Katherine Braunlich, DO; kbraunlich2@gmail.com

Abstract

Agiolymphoid hyperplasia with eosinophilia (ALHE), also known as epithelioid hemangiomia (EH), is an uncommon, benign vascular proliferation characterized by an inflammatory infiltrate composed primarily of eosinophils. In the current literature, there is little evidence of ALHE occurring on the lower extremities. We describe a rare case of ALHE occurring in a 48-year-old Caucasian female who presented with a pruritic, tender, palpable lesion on the right posterior thigh. Histopathological examination revealed increased dermal vasculature comprised of thick-walled blood vessels with protuberant hobnail endothelium. The lesion was diagnosed as agiolymphoid hyperplasia with eosinophilia, and the patient was referred to a Mohs surgeon for local excision.

Introduction

Agiolymphoid hyperplasia with eosinophilia (ALHE), also known as epithelioid hemangiomia (EH), is a rare, benign vascular proliferation first described by Wells and Whimster in 1969. ALHE is characterized by a proliferation of epithelioid cells in thick-walled blood vessels. Clinically, ALHE appears as smooth, violaceous, red-brown papules or nodules in the head and neck region, most commonly near the ears. The lesions can be solitary or numerous and range in size from 1 cm to 10 cm. Generally, the lesions are asymptomatic, though patients occasionally present with a pulsatile sensation, pruritus, or bleeding. ALHE rarely causes systemic complications, unlike the related entity Kimura disease, which is strongly linked to nephropathy and the resulting nephrotic syndrome with proteinuria. Both conditions are eosinophilic dermatoses, but Kimura’s disease is associated with increases in serum eosinophil count and immunoglobulin E (IgE) level. Approximately 20% to 21% of patients with ALHE have eosinophilia, but without elevated IgE. As a result, peripheral eosinophilia is not required to make the diagnosis of ALHE.

There are several theories on the pathogenesis of ALHE, though the specific etiology remains elusive. Current literature suggests ALHE is a reactive process, proposing trauma, infection or hormonal/autoimmune disorders as causes. In many cases, the base of the lesion shows evidence of tortuous vasculature on histology, suggesting arteriovenous shunting plays a role in the pathogenesis of ALHE.

ALHE is reported most frequently in females between 20 years and 40 years old. The most common age at presentation is between 30 years and 33 years. Children and the elderly are rarely afflicted with ALHE. Along with clinical findings, histology is the principal diagnostic component. The fundamental histopathologic finding in ALHE is vascular proliferation lined by epithelioid endothelial cells. The endothelial cells are enlarged, with abundant eosinophilic cytoplasm and large nuclei with intermittent hobnailing or a cobblestone appearance. ALHE is also characterized by an inflammatory infiltrate often comprised of histiocytes, mastocytes and, most notably, eosinophils. Eosinophils have been found to account for up to 50% of the ALHE infiltrate. Ordinarily, ALHE does not resolve spontaneously, and the mainstay of treatment is surgical excision.

Case Description

A 48-year-old Caucasian female presented with concerns about her psoriasis and a pruritic, tender, palpable lesion on the right posterior thigh. According to the patient, the lesion had been present for two years and had not undergone previous treatment. The patient was born and living in the United States. A comprehensive review of systems was negative, and she denied trauma to the area. She denied a history of alcohol or recreational drug use but acknowledged smoking one pack of cigarettes per day for the last 30 years. Her medical history included psoriasis, arthritis and asthma, as well as an allergy to IV radiocontrast media. Recent routine blood work included a complete blood count (CBC) and urine analysis (UA) without pathology. Her serum eosinophil count was within normal limits (0.1 [0.0-0.7]).

Dermatological examination revealed a 15 mm, red-brown, dome-shaped, firm subcutaneous nodule located on the right proximal posterior thigh (Figure 1). The remainder of the skin exam revealed erythematous plaques with silver scale distributed extensively over the patient’s body. The patient was found to have severe generalized plaque psoriasis covering 34% of her total body surface area.

Following punch biopsy, histopathological examination revealed parakeratosis with psoriasiform epidermal hyperplasia and an inflammatory interstitial infiltrate extending from the dermis into the subcutaneous tissue (Figure 2). Also present was increased dermal vasculature comprised of thick and thin-walled blood vessels with protuberant hobnail endothelium (Figures 3, 4), and a mixed inflammatory infiltrate comprised of lymphocytes, histiocytes, plasma cells and many eosinophils (Figure 5). CD34 immunohistochemical stain identified dermal vessels with endothelial hyperplasia within the
Angiolymphoid hyperplasia with eosinophilia is an uncommon, benign vascular disease commonly presenting as subcutaneous nodules on the head and neck. Current literature describes very few cases of ALHE involving the lower extremities. A literature search turned up only three reports: The first involved the distal femoral entrapment of the ulnar nerve; the second was a presumed but unconfirmed case of ALHE in the posterior tibial artery; and the third was a single lesion on the thigh and inconclusive histologically, displaying features of both Kimura’s disease and ALHE. 4,8,18

ALHE and Kimura’s disease can be differentiated on pathology. ALHE is characterized by the occasional lymphoid follicle, whereas Kimura’s disease is known for well-formed lymphoid follicles in addition to the eosinophilic infiltration. 3,9

Since the first reported cases of ALHE, most cases have occurred within the cephalic region. The predilection for the head and neck, specifically the periauricular region, is well noted throughout the literature. 3,5,9,13 All nine of Wells and Whimster’s first reported cases involved the head and neck. 1 Additional sites of involvement include the hands, shoulders, breasts, oropharynx, orbit, ocular adnexa, upper extremities and genitalia. 1,5,9,13 There are rare reports of extracutaneous involvement, including of the lungs, bone, colon and heart. 3,10,15

ALHE rarely undergoes spontaneous resolution, and the mainstay of treatment is surgical excision. Recurrence is observed in one-third of cases. 5,8,9,20 Lembo et al. reports local recurrence may be as high as 50 percent after standard surgical excision. 17 Due to recurrence, other, less-invasive therapeutic modalities have been explored, including topical tacrolimus, isoretinoin, imiquimod and interferon alpha. 5,17-24 Intrallesional corticosteroid therapy has shown better aesthetic results than topical, with recurrence rates comparable to surgical excision. 6,47 Surgical excision, however, remains the treatment of choice, and when the lesion is completely excised, recurrence is rare. 1,3-9,12,16,17,25,26

Conclusion

Angiolymphoid hyperplasia is an uncommon lesion characterized by endothelial cell proliferation surrounded by an inflammatory infiltrate comprised primarily of eosinophils. The most common location for lesion development is the head and neck area. We recommend clinicians reassure patients and families that the vast majority of ALHE cases are entirely benign, with no malignant transformation reported. 3,9

In our case, ALHE involved the lower extremity, an unusual clinical presentation. Histopathological findings, however, were typical of ALHE. The patient underwent Mohs excision of the lesion and is following up routinely to evaluate for new lesions and receive continued treatment of her psoriasis.

References


AGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA ON THE LOWER EXTREMITY: CASE REPORT WITH BRIEF REVIEW


Brooke-Spiegler Syndrome: A Case Report

Sarah Malerich, DO,* Danielle R. Lazzara, DO,** Alpesh Desai, DO***

*Dermatology Resident, 1st Year, Dermatology South Texas/University of North Texas Health Science Center, Houston, TX
**Rowan University School of Osteopathic Medicine, Stratford, NJ
***Program Director, Dermatology Residency, Dermatology South Texas/University of North Texas Health Science Center, Houston, TX

Disclosures: None
Correspondence: Sarah Malerich, DO; sarahmalerich@gmail.com

Abstract

Brooke-Spiegler syndrome (BSS) is a rare, inherited, autosomal-dominant genodermatosis characterized by the development of multiple adnexal cutaneous tumors including spiradenomas, cylindromas, spiradenocylindromas, trichoepitheliomas, epidermoid cysts, and milia. We present a case of Brooke-Spiegler syndrome with possible malignant transformation of a benign tumor.

Introduction

Brooke-Spiegler syndrome (BSS) is a rare, inherited, autosomal-dominant genodermatosis characterized by the development of multiple adnexal cutaneous tumors including spiradenomas, cylindromas, spiradenocylindromas, trichoepitheliomas, epidermoid cysts, and milia.5,6,7,9,10 Mutations identified in the cylindromatosis (CYLD) gene, mapped to chromosome 16q12-q13 via locus analysis, leads to aberrant regulation of putative stem cells of the follicular-sebaceous-apocrine unit, predisposing individuals to the gradual development of skin appendage neoplasms.3,4,10

BSS has variable expressivity and incomplete penetrance; however, a high penetrance for adnexal tumors is observed in relation to increasing age of mutation carriers.3,7 A spectrum of phenotypic presentations has been described in association with CYLD mutations, including familial cylindromatosis (FC) and multiple familial trichoepitheliomatosis (MFT), clinically defined by cutaneous cylindromas and trichoepitheliomas, respectively.4,7,9,10 Rarely, patients may present with solely cutaneous spiradenomas or spiradenocylindromas.10 Although FC, MFT, and BSS were classically considered distinct entities, BSS is now widely accepted to encompass all clinical variants, as the syndromes exhibit clinical, histological, and genetic overlaps consistent with phenotypic variations of the same disease.3,4,9,10 In fact, intrafamilial phenotypic variability amongst individuals with the same germline CYLD mutations has been frequently documented, further demonstrating the variability of BSS and a lack of genotype-phenotype correlation.7

Cutaneous tumors have a predilection for the face and neck and can range in number from 10 to several hundred, and thus can be physically disfiguring and psychologically distressing.5,7 Apart from cosmetic concerns, tumors in close proximity to the eyes and ears can impair the senses.1,5,10 Progressively growing cylindromas or spiradenomas overlaying the external ear can occlude the external auditory canal, resulting in deafness.9 Benign adnexal tumors have the potential to undergo malignant transformation, which is notably more common in BSS than in the sporadic form.2,10 Extracutaneous, morphologically similar neoplasms can also arise in the salivary glands in association with BSS.1,2,4,7,9,10,12,13 It is highly recommended for patients presenting with multiple adnexal neoplasms to be referred for genetic testing and receive regular dermatologic examination to best manage therapy and monitor for malignant transformation of tumors.1,7,10

Case Report

An 84-year-old female with a medical history of multiple firm, pink nodules with surface telangiectasias involving the forehead, external ears, and scalp presented to our clinic with the complaint of painful nodular growth (Figure 1). The patient had a family history of similar lesions in her brother, sister and mother.

A 1.6 cm x 0.5 cm biopsy was taken from the largest lesion. Histologic findings showed multiple nests of basaloid cells forming a jigsaw-like pattern with scant stroma surrounded by eosinophilic, hyaline-rich sheaths, consistent with cylindroma (Figures 2, 3 [p. 21]).

The patient returned to our clinic two weeks later complaining of continued growth of the lesion with increased pain. An excision was performed, measuring 2.7 cm x 2.2 cm x 1.3 cm. The pathology report, discussed at dermatopathology consensus conference, was read as adnexal neoplasm, favoring cylindroma, with re-excision recommended to rule out malignant transformation of the benign tumor.

The patient was referred to facial plastic surgery for complete wide-margin excision and reconstruction. At the time of visit, three additional biopsies were taken from sites the patient deemed bothersome and were diagnosed as benign spiradenomas (2) and cylindroma (1). Histopathological examination revealed a lymphocytic cell population with basaloid cells arranged in rosettes, characteristic of spiradenomas, while the other tumor exhibited discrete nests in a jigsaw-puzzle pattern, representing a cylindroma. Given the patient’s presentation of multiple adnexal cutaneous tumors,
Subjective complaint of painful tumors is indication for excisional removal.4,6,10,11 Despite occurrence, malignant adenexal neoplasms reported in the literature include cylindrocarcinoma, spiradenocarcinoma, and spiradenocylindrocarcinoma.3,5,6,9,11,12,13,14,15 Akgul et al. identified a total of 72 well-documented cases of cylindrocarcinoma via Pubmed database search, and of those cases, 10 patients developed lymph node and distant metastasis.16 Rare reports of trichoepithelioma degeneration to basal cell carcinoma have also been described.1,2,6,9,10 Extremely rare are reports of BSS associated with minor and major salivary gland tumors.17,12,13,15,17,18 Membranous basal cell adenoma is a dermal-analogue salivary gland tumor histologically identical to cutaneous cylindroma, which accounts for less than 2% of all salivary gland tumors. Basal cell adenocarcinoma, the malignant equivalent of membranous basal cell adenoma, can also manifest in BSS cases.4,12 Kazakov et al. reports an unusual case of a 68-year-old woman with a parotid gland tumor identical to cutaneous spiradenoma with partial transformation to basal cell adenocarcinoma.12 Notably, the patient lacked features of BSS, and CYLD gene analysis displayed polymorphisms.12 CYLD mutations have been identified in parotid-gland basal cell adenocarcinoma. Bowen et al. describes a BSS patient with a determined CYLD-6 mutation presenting with bilateral parotid gland basal cell adenocarcinoma, evidencing syndrome association with germline CYLD mutations and the development of salivary gland malignancy.4 Cases of adeno cystic carcinoma have also been reported.10,14 Despite undetermined patient risk factor, salivary gland tumors should be suspected in individuals with cutaneous tumors localized to the face in close proximity to salivary glands.12 BSS patients are particularly susceptible due to CYLD mutations and should be evaluated for salivary gland tumors, so close dermatology follow-up is highly recommended for individuals with BSS.2,7,10

BSS tumors share histopathologic features with sporadic tumor forms.17 It is not unusual for a single biopsy specimen to exhibit multiple neoplastic morphologies or histologic evidence of hybrid tumors, such as the spiradenocylindroma, when associated with the syndrome as opposed to the sporadic form.5,8,12 In fact, cylindromas and spiradenomas are considered histologic extremes of the same neoplasm.9 Despite histological overlap, characteristic features distinguish these tumors. Cylindromas are well-circumscribed dermal nodules formed by monomorphic, basoloidal cells arranged in a jigsaw-puzzle pattern and surrounded by eosinophilic basement membrane, hyaline material,6,10,15 Central cells are paler than pilosebaceous peripheral cells, creating dual epithelial cells.6,10 In contrast, spiradenomas are comprised of lymphocytes and lack the jigsaw arrangement typical of cylindromas.12 Spiradenomas are dermal nodules composed of small, dark, basoloidal epithelial cells arranged in a rosette pattern. The other prominent cell type is a large, pale-colored cell found at the center of the tumor nests.5,8,10,13 Trichoepitheliomas are characterized by basoloidal pilosebaceous cells forming nests or cribriform patterns surrounded by fibroblast and collagen bundle-rich stroma.3,4,13,15 Multiple horn cysts are sometimes present.11

Malignant transformation of cutaneous adenexal tumors is confirmed by histology and often requires a whole-tumor specimen to appreciate the overall architecture of the neoplasm, which displays heterogeneity, with benign portions accounting for 5% to 40% of the tumor.11,13 Transition from benign preexisting tumor to malignant pathology can be gradual or abrupt.10 Four main patterns of malignant cutaneous neoplasms are recognized: low-grade salivary gland-type basal cell adenocarcinoma-like pattern; high-grade salivary gland-type basal cell adenocarcinoma-like pattern; sarcomatoid (metaplastic) carcinoma; and invasive adenocarcinoma, not otherwise specified.10,12,13 In low-grade salivary gland-type basal cell adenocarcinoma, small-to-medium basoloidal cells form nodules varying in shape and size, with peripheral palisading occasionally present.10 Cell nuclei are small or absent, cytoplasm is scant and an infiltrative growth pattern is appreciated. High-grade pattern malignant tumors display medium- to large pleomorphic basoloidal cells forming an infiltrative pattern of confluent sheets and nodules. The cells have vesicular nuclei, scant cytoplasm, and high mitotic count. Loss of dual epithelial cells and lymphocytes characteristic of the precursor benign tumor are other distinguishing features.9,10

Treatment of BSS is mainly aimed to improve cosmesis and includes resurfacing modalities such as thermal electrodessication, cryotherapy, dermabrasion, trichloroacetic acid, retinoic acid, and erbium-YAG/carbon dioxide (CO2) laser.1,3,8,17,18 Resurfacing therapy is most appropriate and effective for trichoepitheliomas; however, patients will need repeat treatments due to recurrence of lesions.17 Surgical excision of tumors with wide local excision or Mohs micrographic surgery is most effective and preferred due to potential malignant transformation of benign neoplasms.17,19 Tumors are quite vascular and require a substantial blood supply to support growth, posing a challenge to the excision of large, confluent neoplasms.5,10 Jatan et al. reports use of pre-operative radiological embolization to minimize bleeding and maximize extent of tumor excision.19 Radiotherapy has been
Causative therapy for BSS remains under investigation. Recent studies have revealed impaired tropomyosin kinase (TRK) signaling associated with CYLD mutations, as well as overexpression of TRK in cylindroma cells. Continued genetic studies are necessary to further develop effective, causative therapies that significantly improve patient outcomes beyond the symptomatic relief provided by current treatment modalities.

References


A Case of Cutaneous Metastatic Renal Cell Carcinoma to the Scalp

Lacey Roybal, DO,* Keith MacKenzie, DO,** Karen Warschaw, MD***

*Traditional Rotating Intern, Good Samaritan Regional Medical Center, Corvallis, OR
**Board-certified Dermatologist, MacKenzie Dermatology, Prescott, AZ
***Board-certified Dermatopathologist, Aurora Diagnostics, Scottsdale, AZ

Disclosures: None
Correspondence: Lacey Roybal, DO; lroybal@samhealth.org

Abstract
Renal cell carcinoma (RCC) is the most common malignant genitourinary cancer in adults. It has been shown to be resistant to chemotherapy and radiation and can metastasize to virtually any organ site; however, cutaneous metastasis is rare. We present a case of cutaneous renal cell carcinoma metastatic to the scalp. It is important for the dermatologist to recognize the histopathologic and clinical features of cutaneous RCC in order to properly diagnose and treat patients and refer them for appropriate further management.

Introduction
Renal cell carcinoma (RCC) is among the top ten most prevalent cancers in adults, accounting for 2% to 3% of all malignant diseases. The American Cancer Society predicted about 62,000 new cases of kidney cancer in the United States in 2016. The average age at diagnosis is 65, and men have a higher risk for developing RCC than women. Renal cell carcinoma makes up the majority of kidney tumors, accounting for 80% to 90% of all malignant kidney cancers. The most common presenting symptoms of renal cell carcinoma are hematuria, abdominal pain, and a palpable flank mass, though fewer than 10% of patients present with all three symptoms. The greatest risk factors contributing to the development of RCC are cigarette smoking, high body mass index, and hypertension. RCC is known to present without early warning signs and has proved resistant to chemotherapy and radiation. With the frequent use of axial imaging, greater than 70% of RCC are found incidentally on imaging studies. At the time of presentation, metastatic disease is present in approximately 30% of patients, most commonly in the lymph nodes, lung, bone, liver, adrenal gland, contralateral kidney and brain. Metastatic disease typically occurs within the first five years after diagnosis, though cases have been reported of systemic spread decades after treatment.

Case Report
A 77-year-old Caucasian male presented to the dermatology office with a bleeding bump on his scalp. He reported the lesion had been present for a few years, and denied pain or rapid growth. The patient’s past medical history included atrial fibrillation, hypertension, and RCC status post nephrectomy in 2013. On physical examination, he was noted to have male pattern baldness and a 0.7 cm, crusted, brown-purple papule on the right posterior vertex of his scalp (Figure 1).

The clinical differential diagnosis included metastatic RCC, pigmented basal cell carcinoma, a vascular lesion and melanoma. A shave biopsy of the lesion was performed, and histopathology revealed sheets and nodules of atypical clear cells with large vascular spaces filled with erythrocytes (Figures 2, 3). The tumor cells stained positive with RCCma (Figure 4), PAX-8 (Figure 5), PAX-2 and EMA, and negative for CK7 and CK20. A diagnosis of metastatic clear-cell renal cell carcinoma was made.

Discussion
Renal cell carcinoma is known for its aggressive nature and ability to metastasize to unique sites and mimic other cutaneous lesions. There are five types of kidney carcinomas distinguished histologically, including clear cell and papillary tumors (originating from the proximal tubule), oncocytic/chromophobe tumors (originating from the cortical collecting duct), and collecting duct tumors (originating from the medullary collecting duct). Clear cell carcinomas are the dominant tumor type, making up 75% to 85% of renal carcinomas. The clear cells are polygonal or round with abundant cytoplasm containing cholesterol, glycogen and phospholipids surrounded by a network of fibrovascular stroma. Most clear cell tumors are characterized by a deletion of the alleles of chromosome 3p25, the von Hippel-Lindau gene (VHL). VHL is a tumor suppressor gene located at chromosome 3p25.

Figure 1. Papule on right posterior vertex of scalp.

Figure 2. Tumor nodule with large vascular spaces and lobules of clear cells.

Figure 3. Higher-power view showing tubules of clear, glycogenated cells with large vascular spaces and hemorrhage.

Figure 4. Positive RCCma stain.

Figure 5. Positive Pax-8 stain.
gene whose loss of function contributes to tumor development, including VEGF expression. There are genetic syndromes, such as von Hippel-Lindau syndrome and tuberous sclerosis, that predispose individuals to the development of clear-cell renal cell carcinomas. However, these syndromes make up a small proportion of clear cell RCC, and the majority occur without associated genetic disease.

Cutaneous metastasis of renal cell carcinoma is rare (3.4%). The four mechanisms for cutaneous metastasis are direct invasion from an underlying tumor, lymphatic extension, hematogenous spread and implantation of neoplastic cells from a procedural scar. Genitourinary malignancies' most common cutaneous metastasis site is abdominal skin, particularly for non-RCC tumor types. However, renal cell carcinoma more frequently affects the skin of the head and neck. The vascular nature of the tumor may contribute to RCC's ability to spread to distant sites, mostly via hematogenous extension. In one major retrospective study of patients with cutaneous metastasis, 4.6% of patients with metastatic RCC had cutaneous metastasis, with the majority spread to the scalp. This finding supports previous studies showing a disproportionate number of cases of RCC metastasis to the scalp.

Most cutaneous metastases occur as nodules, typically multiple. Due to their red to purple color, the nodules of metastatic RCC are often mistaken for hemangiomas, pyogenic granulomas, or Kaposi's sarcoma on examination. The morphology of the lesions imitates that of cutaneous horns, lymphoma, abscesses and cutaneous cysts, similar to the findings in our case, establishing a broad differential and the need for histopathologic studies. A punch biopsy or excisional biopsy is recommended for diagnosis of metastatic RCC. As the carcinoma primarily invades the dermis, a superficial shave biopsy may be too shallow to provide sufficient tissue for diagnosis.

Histopathology
The histology of metastatic lesions typically maintains similarities to the primary lesion, but the presence of lymphatic and vascular infiltration, anaplasia and poor differentiation are clues that a lesion is metastatic. Immunohistochemistry (IHC) is an invaluable tool for differentiating clear cell tumors of similar morphology and unknown origin. IHC markers helpful in diagnosing metastatic RCC include RCC monoclonal antibody (RCCma), epithelial membrane antigen (EMA), PAX-2 and PAX-8. Both markers of the human paired boxed gene family and important in the transcription of renal cell lines, are used most frequently due to their greater sensitivity and specificity in RCC. RCCma is well established and utilized as a marker for clear cell RCC, as it stains positive in approximately two-thirds of RCC cutaneous metastases. RCCma is highly specific and is not expressed in other clear cell malignancies of the skin (such as clear cell hidradenoma/carcinoma). The majority of RCC cells also express EMA. In our case, the tumor stained positive for PAX-2, PAX-8, EMA and RCCma, indicating clear cell RCC as the likely source of the tissue. In our study, we also utilized CK7, a marker for Paget's disease and non-G1 adenocarcinomas like lung, breast, bladder and pancreas, and CK20, a marker for Merkel cell carcinoma and gastrointestinal adenocarcinomas like colon cancer, to help rule out other potential sources of metastasis. Only 10% of RCC express either CK7 or CK20. Both markers were negative in our tissue sample.

Conclusion
Cutaneous metastatic renal cell carcinoma poses a diagnostic dilemma in dermatology. Clinically, it can mimic many other tumor types and vascular lesions. A multidisciplinary approach to diagnosis and treatment is important, as patients will need referral to oncology and urology to manage the condition. It is important to be able to recognize the clinical and pathologic signs of metastatic cutaneous lesions, as they may be the first indication of underlying malignancy.

References
Hepatocellular carcinoma (HCC) is a malignant primary liver cancer often associated with a background of hepatitis B or C viral infection. Recently, other risk factors such as obesity, diabetes mellitus, and nonalcoholic fatty-liver disease have been recognized. In a small portion of patients, HCC metastasizes to the lung, intra-abdominal lymph nodes, bone, or adrenal gland. HCC rarely develops cutaneous metastases, and it is especially uncommon to acquire metastases to the skin of the face. Diagnosis of HCC generally occurs before metastasis to distant sites, and treatment is often limited to palliative measures once distant metastases occur. We present a patient with a history of fatty liver diagnosed with HCC after cutaneous metastasis to the face.

Abstract
Hepatocellular carcinoma (HCC) is a malignant primary liver cancer often associated with a background of hepatitis B or C viral infection. Recently, other risk factors such as obesity, diabetes mellitus, and nonalcoholic fatty-liver disease have been recognized. In a small portion of patients, HCC metastasizes to the lung, intra-abdominal lymph nodes, bone, or adrenal gland. HCC rarely develops cutaneous metastases, and it is especially uncommon to acquire metastases to the skin of the face. Diagnosis of HCC generally occurs before metastasis to distant sites, and treatment is often limited to palliative measures once distant metastases occur. We present a patient with a history of fatty liver diagnosed with HCC after cutaneous metastasis to the face.

Introduction
Hepatocellular carcinoma (HCC), the most common primary liver cancer, is a malignant cancer that usually develops in a setting of chronic inflammation. The development of HCC is frequently a product of cirrhosis, which primarily occurs as a result of risk factors such as hepatitis B or C viral infection. Although significant risk factors for acquiring HCC, such as hepatitis B or C viral infection, have been well established, evidence is mounting for other risk factors such as obesity, diabetes mellitus, and nonalcoholic fatty-liver disease. It has been reported that HCC affects six per 100,000 people and is the most rapidly increasing cause of cancer-related death in the United States. With the rise of metabolic syndrome and associated conditions in the United States, HCC is becoming a significant source of morbidity and mortality.

The most common presenting symptoms of primary liver cancers are abdominal pain and weight loss. Patients regularly have other symptoms like fatigue or malaise, and infrequently present with a paraneoplastic syndrome or cutaneous features. A diagnosis of HCC coupled with metastasis to sites outside the liver occurs in approximately 5% to 15% of patients. In descending order, the lung, intra-abdominal lymph nodes, bone, and adrenal gland are the most common sites of metastasis. Internal malignancies rarely metastasize to the skin, and of those that do, HCC makes up only a small percentage. In one study reviewing 12,146 cases of internal malignancies, only 124 (1.02%) patients were found to have cutaneous metastases. HCC was found to have a rate of metastasis to the skin of 0.34%.

A wide range of treatment options are available for HCC. Tumor resection, radiofrequency ablation, and liver transplantation are some of the more radical treatment options. Treatments with a more palliative intention include trans-arterial chemoembolization, systemic chemotherapy, and intra-arterial radioembolization. Although many treatment options exist, median survival is about six to 20 months from diagnosis. HCC's high mortality rate highlights the importance of accurate and timely diagnosis. In this case report, we present a patient diagnosed with HCC after cutaneous metastasis to the face.

Case Report
After being referred from an urgent care facility, a 62-year-old Caucasian male presented with a skin lesion located on the superior medial forehead. The lesion had been present and slowly growing for four months. Mild bleeding occurred after scratching or picking the lesion, which led him to seek medical care. He had not been treated for this lesion before. Past medical history was significant for hypertension, dyslipidemia, elevated liver function tests, fatty liver (diagnosed two years prior to presentation), glucose intolerance, and basal cell carcinoma. Social history was significant for smoking approximately two cigarettes per day for 40 years, and drinking two-plus drinks per night for an unknown period of time. Other history was noncontributory. Medications were furosemide, losartan, and levothyroxine. Review of systems was significant for easy bleeding, easy bruising, and chronic lymphedema.

Physical exam showed two erythematous papules, one located on the superior mid-forehead, measuring 0.5 cm, and the other on the right nasal infratip, measuring 0.4 cm. The patient was not in acute distress, and the lesions were not actively bleeding. Two shave biopsies were conducted under the tentative diagnosis of a neoplasm of uncertain behavior. Each biopsy showed similar histologic findings strongly suggesting a carcinoma. A strong suggestion of hepatocytes was implied on routine sections by interconnected cords of malignant cells with a low nuclear-to-cytoplasmic ratio (Figures 1-3). An intracytoplasmic, green-brown material was also found, which further supported the finding of hepatocytes. On immunohistochemical staining, the cells were negative for cytokeratin 7, cytokeratin 20, and hepatocyte marker hepatocyte paraffin 1 (Hep Par 1) (Figure 4). The results strongly supported a diagnosis of metastatic HCC. A subsequent Fouchet’s stain confirmed intracelular bile, establishing the diagnosis of metastatic HCC (Figure 5).

Due to poor wound healing, multiple visits occurred after the initial diagnosis of metastatic HCC. The patient was referred to oncology, and CT revealed a 5.2 cm hypervascular mass and possibly another 1 cm hypervascular lesion in the liver. He was started on sorafenib 200 mg PO BID. The patient passed away within a year.
Discussion

HCC is an important source of morbidity and mortality; in the United States, it is the most rapidly increasing cause of death related to cancer. Cutaneous metastasis of HCC is rare. These characteristics underscore the importance of the case presented here. This case is delineated from the small number of other cutaneous metastases of HCC by a few other features. First, many of the cases of cutaneous metastasis of HCC have occurred after the initial diagnosis of the disease. Interestingly, almost all reported cases of cutaneous metastases and cutaneous metastasis of HCC have occurred with a background of hepatitis B or C infection. The patient in this case was diagnosed after the cutaneous presentation, and he was not documented to have a history of hepatitis B or C infection. The patient’s HCC was attributed to cirrhosis from a combination of fatty liver and possibly a small amount of alcohol use. In addition, only a few cutaneous metastatic HCC cases have reported lesions on the face.

Few cases have reported HCC metastasis to the nose, but reports have documented that men older than 50 years old with cutaneous metastasis of HCC have a higher predilection for HCC metastasizing to the nose. It is not clear why this seems to occur in men older than 50 years. A possible theory is that areas with more sun exposure and UV radiation, such as the face, undergo additional changes in protein structures, which may augment HCC cells’ ability to bind to receptors in those areas.

The presented case reminds clinicians to be vigilant in their awareness of rare but increasingly common diagnoses. The possibly relevance of a history of fatty liver, as elicited in this case, accentuates its importance in Western societies, as fatty liver is becoming progressively more common. In this case, chronic fatty liver was likely the main trigger of cirrhosis, which led to the HCC. Since the link between HCC and fatty liver is becoming stronger, it is reasonable to assume that more cases of HCC may be seen in the future throughout Western societies.

Although skin metastasis of HCC is rare, with more cases of HCC we may see more skin metastases. Furthermore, awareness of the possibility that HCC can metastasize to the skin could facilitate timely diagnoses and treatment. Bolstering the importance of this awareness is the fact that the prognosis of HCC is grim, with a median survival of six to 20 months. Even if treatment becomes palliative, a longer duration of palliative care can drastically improve end-of-life quality. While we can’t know how much longer the presented patient would have survived had he been diagnosed earlier, it is noteworthy that he was diagnosed with fatty liver two years before presentation, and he did not follow up on the presence of elevated LFTs, all of which occurred before the cutaneous metastasis.

Conclusion

HCC is an increasingly common cause of cancer-related death. Cutaneous metastasis from HCC is exceedingly rare, and almost all cases occur after a background of hepatitis B or C. The presented case differs in that the patient had a history of chronic fatty liver. He was diagnosed with HCC only after cutaneous metastasis. Metastatic cutaneous HCC to the nose seems to occur more often in men over the age of 50, though it is not understood why. With fatty liver becoming progressively more common in Western societies, it is important to be aware of its presentation in order to diagnose and treat the condition in a suitable fashion.

References


Disseminated Mycobacterium Tuberculosis with Ulceronecrotic Cutaneous Disease Presenting as Cellulitis

Kelly L. Reed, DO,* Rachel M. White, DO,** Nektarios Lountzis, MD***

*Dermatology Resident, Lehigh Valley Health Network, Allentown, PA
**Traditional Rotating Intern, Largo Medical Center, Largo, FL
***Attending Physician, Dermatology Residency, Lehigh Valley Health Network, Allentown, PA

Disclosures: None
Correspondence: Rachel M. White, DO; rachelwh@pcom.edu

Abstract
Cutaneous tuberculosis is a rare manifestation of infectious tuberculosis caused by invasion of the skin by Mycobacterium tuberculosis. Tuberculous cellulitis is a rare type of cutaneous tuberculosis with cellulitis–like symptoms. Only eight cases of tuberculous cellulitis have been reported in the literature. We report a case of tuberculous cellulitis in a patient taking chronic systemic steroids for polymyalgia rheumatica. Findings on all of the reported cases of tuberculous cellulitis are summarized.

Introduction
Tuberculosis (TB) is an infectious disease most commonly caused by Mycobacterium tuberculosis and primarily affecting the lungs. TB can affect organs in the central nervous system, lymphatic system and circulatory system, as well as the skin.1 According to the World Health Organization (WHO), in 2013 there were 9.0 million cases of tuberculosis, and 0.8 million of the new cases were extrapulmonary.2 Cutaneous TB is a rare manifestation of TB caused by invasion of the skin by M. tuberculosis.3 Cutaneous TB occurs through direct infection of skin from an exogenous or endogenous source. It can also occur from an allergic response to tubercle bacilli or their metabolites, called tuberculid.4 Only eight cases of TB cellulitis, a rare type of cutaneous TB with cellulitis–like symptoms, have been reported.1 We present a case of tuberculous cellulitis in a patient with polymyalgia rheumatica (PMR) who was taking chronic systemic steroids.

Case Report
An 83-year-old Hispanic female with a past medical history of polymyalgia rheumatica (PMR) was treated at the hospital for a non-ST–segment elevation myocardial infarction and was noted to have redness and swelling of the right lower extremity, which the patient reported had been present for five months. She had been treated with multiple courses of antibiotics with no response. She denied fever, cough, night sweats, fatigue or other systemic symptoms. Additional past medical history included coronary artery disease, diabetes mellitus type 2, hypertension, atrial fibrillation, asthma, and hyperlipidemia. She had resided in Puerto Rico but recently moved to the United States. Her social history included > 100 pack years of smoking tobacco. The patient’s pertinent medications included chronic low dose prednisone at 5 mg daily for many years to treat her PMR.

Physical exam revealed multiple red to purple, painful, indurated plaques associated with pitting edema extending along the right leg and remainder of right lower extremity and culture of bronchial lavage revealed Mycobacterium tuberculosis complex. The patient tested positive on QuantiFERON®-TB Gold and was diagnosed with disseminated Mycobacterium tuberculosis resulting in tuberculous cellulitis. Treatment included topical wound care and quadruple antibiotic therapy with rifampin, isoniazid, ethambutol, and pyrazinamide.

Discussion
Cutaneous tuberculosis manifests in a variety of clinical presentations and is caused by Mycobacterium bovis, bacillus Calmette-Guérin (BCG), or most commonly the acid-fast bacillus (AFB) M. tuberculosis.3 Cutaneous tuberculosis accounts for less than 1% to 2% of all cases of TB.5 Infection can occur through primary exogenous inoculation via direct implantation of mycobacterium into the skin.1 Secondary spread occurs endogenously through hematogenous dissemination, proliferation via contiguous lymph nodes or direct extension to the skin from an internal source, most commonly lung infection.3,4

Another manifestation of cutaneous TB, known as a tuberculid, occurs due to an allergic reaction to the bacteria or one of its metabolites.2 Tuberculids are characterized by the absence of mycobacterium in the skin. Cutaneous tuberculosis is also classified depending on the quantity of acid-fast bacilli...
Clinical presentation of cutaneous tuberculosis is extremely variable and dependent upon both the route of infection and the bacterial load present in lesions. It most often affects elderly, immunocompromised hosts, such as those with HIV or taking immunosuppressive medications like corticosteroids. Clinically, exogenous inoculation causes tuberculous chancres, TB verrucosa cutis, and some cases of lupus vulgaris. Endogenous spread results in scrofuloderma, miliary TB, orificial tuberculosis, and most cases of lupus vulgaris. Tuberculids are reactive conditions that include papulonecrotic lesions, lichen scrofulosorum and erythema induratum. Tuberculous cellulitis, as our patient developed, is an uncommon presentation and does not fit neatly into the aforementioned categories.

Histopathological findings vary depending on the type of infection; however, cutaneous TB characteristically manifests as a mixed inflammatory reaction of the dermis and subcutis comprised of neutrophils, multinucleate giant cells and epitheloid histiocytic granulomas that may display caseation necrosis. The biopsy of our patient’s cellulitis was congruent with these findings, revealing mixed inflammatory infiltrate with granulomatous changes. Diagnosis of cutaneous TB is multifaceted and often includes a combination of purified protein derivative (PPD), interferon-γ release assay, tissue culture, polymerase chain reaction (PCR) for mycobacterial DNA, and tissue culture and/or biopsy with special staining techniques, such as Auramine-Rhodamine, Ziehl-Neelsen or Wade-Fite stain. Our patient’s lesions were positive in tissue culture, Ziehl-Neelsen stain, PCR and interferon-γ release assay.

Our patient’s cutaneous tuberculosis resulted from endogenous spread and presented as a recalcitrant “cellulitis” that deteriorated to an uncommon ulceronecrotic form of the disease. Typically, ulceronecrotic cases are due to tuberculid reactions; however, in this case, the isolation of bacilli on tissue culture favors an active cutaneous infection from hematogenous spread.

With the addition of this report, there are only nine cases of tuberculous cellulitis in the literature. In eight of those cases, the patients were on corticosteroid therapy when they developed tuberculous cellulitis. In one case, the patient was an adolescent recently treated for lymphadenitis TB using triple antibiotic therapy. Therefore, immunosuppression most likely plays an important role in the etiology of the disease. Three out of nine cases had prior infection with different forms of TB. Additionally, one third of tuberculous cellulitis cases have been identified as skin manifestations of miliary tuberculosis. Miliary tuberculosis usually involves diffuse, minute nodules in the bilateral lungs, which our patient did not exhibit. In two reported cases, including this one, chest X-rays showed signs of pulmonary TB. The likelihood of detecting tubercle bacilli in tuberculous cellulitis is high, as demonstrated by 88% of cases being PCR positive, 88% culture positive, and 89% Ziehl-Neelsen stain positive.

Treatment of cutaneous TB is primarily antibiotic therapy with triple or quadruple coverage, based on the culture and sensitivities of the isolated strain of M. tuberculosis. All nine reported cases of tuberculous cellulitis were treated with triple or quadruple therapy including rifampin, isoniazid, pyrazinamide, and ethambutol. All prior reported cases of tuberculous cellulitis drastically improved and eventually resolved with antibiotics.

Conclusion
This case is relevant to clinicians because it increases awareness of cutaneous TB as the presenting symptom of disseminated tuberculosis infections in immunocompromised patients. It also serves as a reminder to maintain a high index of suspicion for such opportunistic infections, specifically in cases of resistant cutulitides, and to complete a thorough patient work-up.

References
An Indigenous Case of Cutaneous Larva Migrans

Conrad Benedetto, DO,* Irini Youssef, BS,** Paul Shitabata, MD,*** Navid Nami, DO****

*Dermatology Resident, 1st year, Western University of Health Sciences, Pomona, CA
**Medical Student, 3rd year, State University of New York Downstate Medical Center - College of Medicine, Brooklyn, NY
***Director of Dermatopathology, Harbor-UCCLA Medical Center, Torrance, CA
****Program Director, Dermatology Residency, Western University of Health Sciences, Pomona, CA

Disclosures: None
Correspondence: Conrad Benedetto, DO; conradbe@pcom.edu

Abstract
Cutaneous larva migrans (CLM) is an infection caused predominantly by the Ancylostoma hookworm, most commonly found in tropical and subtropical areas. The hookworm is acquired through skin contact with soil contaminated by larvae-infested dog or cat feces. Although most U.S. cases are described in patients with a travel history, a few cases of indigenous infections have been reported in patients who cohabitate with canines and felines, whose intestines may be inhabited by the nematode. Once shed into sand or soil, the ova of Ancylostoma larvae require a warm and humid climate to develop into infective filariform larvae. We describe a patient with no travel history who presented to our Southern California clinic with symptoms of CLM.

Introduction
Cutaneous larva migrans (CLM) was first described by Lee in 1874 as a “creeping eruption.” The classic clinical feature of the disease is a serpiginous or linear, erythematous, elevated tract that migrates in an irregular pattern. In 1926, Kirby-Smith et al. were the first to recover nematode larvae from biopsies of patients with creeping eruptions. CLM is caused by the tropical hookworms Ancylostoma braziliense, Ancylostoma caninum, and Uncinaria stenocephala, which inhabit the intestines of domestic animals, including dogs and cats. CLM is acquired via direct contact with soil or sand contaminated with larval eggs of these parasites. The disease is endemic in developing regions, particularly in tropical areas like Central and South America, India, and Africa. Cases seen in the United States are almost always associated with recent travel to endemic regions. We describe a native case of CLM, diagnosed in a patient with no recent history of travel outside the United States.

Case Report
A 59-year-old man with a past medical history of diabetes mellitus type 2 and hypertension presented with a pruritic eruption on the hands and feet of several weeks’ duration. He denied recent travel prior to the onset of the lesions, and no other members of his household were affected. He admitted to having a cat in his home, and reported the cat was healthy.

Physical examination revealed multiple erythematous papules and serpiginous raised tracts on the patient’s feet and hands (Figure 1). Low-power histopathologic examination of a lesion on the right medial foot revealed acral skin with intraepidermal vesicles consistent with parasitic burrows (Figure 2). On higher power, variously sized burrows were noted (Figure 3). On highest power (Figure 4), the burrows were observed to contain collections of neutrophils and eosinophils. Additional features seen histologically with CLM are spongiosis, a lymphohistiocytic dermal infiltrate with eosinophils, and, occasionally, collections of eosinophils within the epidermis and hair follicles. It is unusual for parasites to be seen in the biopsy specimen. Based on the clinical presentation, a diagnosis of cutaneous larva migrans (CLM) was established. He was treated with a one-time dose of 12 mg oral ivermectin, and the eruption had resolved by his two-week follow-up appointment.

Discussion
Cutaneous larva migrans is primarily a clinical diagnosis, most often presenting in those who have traveled to tropical countries. The disease is endemic in coastal states, including Texas and New Jersey, with the highest incidence in Florida. It is caused by the tropical hookworms Ancylostoma braziliense, Ancylostoma caninum, and Uncinaria stenocephala, which inhabit the intestines of domestic animals like dogs and cats. About 20,000 eggs may be produced per female Ancylostoma. Within 56 hours to 66 hours after being shed in the feces of dogs and felines, the eggs undergo two rhabditiform molts to develop into their infective filariform stage. Upon direct contact, the larvae penetrate skin, most commonly of the feet, legs, buttocks or back. Due to their inability to produce the collagenase enzyme essential to invade the basement membrane of the epidermis, the larvae remain limited to the epidermis. Humans serve as dead-end hosts for the larvae. As the larvae migrate through the skin, the host inflammatory response produces an intense pruritic and serpiginous, threadlike reaction that marks the
While CLM is a self-limited disease, with humans as the dead-end hosts, the associated eruption can be distressing to the patient and may last several months. Treatment results in shortening the course of the disease. Treatment options include a single, 400 mg dose of albendazole in adults and children older than two years of age, or 400 mg/day to 800 mg/day (10 mg/kg/day to 15 mg/kg/day in children) for three to five days; a single, 12 mg dose of ivermectin (150 mg/kg in children); or thiabendazole 10% to 15% solution or ointment applied topically three times daily for at least 15 days.

Conclusion
CLM is one of the most frequent helminthic infections diagnosed in travelers returning from areas where the *Ancylostoma* hookworm is endemic, including the Caribbean, Southeast Asia, Central America and Africa. Autochthonous cases of CLM are rare, and the few reported cases describe human skin contacting infected soil, which was likely contaminated with feline or canine feces and then exposed to the humidity and warmth that allow the *A* ovra to develop into infective larvae. Despite the rare occurrence of CLM in the United States, doctors must keep the differential in mind when examining patients exhibiting CLM-like symptoms and cutaneous lesions, even without a history of recent travel. These patients should be educated about wearing protective clothing, including shoes, when outside. Their pets should also be screened and treated for intestinal worms.

References
Intralesional Hyaluronidase with Triamcinolone for Recalcitrant Pretibial Myxedema

Rachel M. White, DO,* Cherise M. Levi, DO, FAOCD, FAAD,** Cindy Hoffman, DO, FAOCD***

*Traditional Rotating Intern, Largo Medical Center, Largo, FL.
**Attending Dermatologist, New York Presbyterian – Columbia University Medical Center, New York, NY.
***Program Director, Dermatology Residency, St. Barnabas Hospital, Bronx, NY.

Disclosures: None
Correspondence: Rachel M. White, DO; rachelwh@pcom.edu

Abstract

Pretibial myxedema resulting in progressively worsening cutaneous induration and expanding nodules can lead to pain, discomfort and functional impairment. Treatment of resistant lesions presents a special challenge whereby topical therapies are insufficient, and systemic therapies are met with poor tolerability, low rate of effectiveness and the added risk of side effects. We report a patient with resistant pretibial myxedema nodules who demonstrated marked overall improvement of great toe lesions, including nodule size and associated discomfort, with repeat injections of hyaluronidase (Vitrase) both with and without triamcinolone acetate.

Introduction

Pretibial or localized myxedema is deposition of dermal mucin resulting from thyroid disease, commonly Graves’ disease, hence the synonymous term “dermopathy of Graves’ disease.” Pretibial myxedema lesions are comprised of hyaluronic acid and can result in fluid retention, edema and elephantiasis. Myxedematous indurated nodules can also cause pain and functional impairment. We present a case in which the patient was debilitated by pretibial myxedematous lesions and failed standard treatment options. We formulated a treatment option, hyaluronidase injections (Vitrase) with and without triamcinolone, that led to functional and cosmetic improvement of the patient’s refractory myxedematous lesions. While hyaluronidase has been briefly described previously in literature, we propose an updated and regulated regimen for use of hyaluronidase injections in refractory pretibial myxedema.

Case Report

A 44-year-old Caucasian female with a past medical history of Graves’ disease, treated with radioactive iodine thyroid ablation, presented to our office with a two-year history of bilateral lower extremity swelling. Her post-procedural hypothyroidism had since been well-controlled with levothyroxine, with no recurrence of initial hyperthyroid-related symptoms. Past medical history also included migraines, as well as multiple unrelated surgical procedures. Periodic laboratory testing revealed normal thyroid stimulating hormone (TSH) levels despite progressively worsening cutaneous lesions. Of note, the patient had persistently elevated thyroid-stimulating immunoglobulins (TSI), consistent with active thyroid dermopathy.

The patient complained of a nine-month history of “raised circles on the right shin and toes.” The right lower extremity lesions were intermittently pruritic, but without associated pain, numbness or paresthesias. She had recent surgical excision of a degenerated sesamoid bone on her right foot, and of masses on bilateral great toes that revealed benign fibroconnective tissue with a myxoid-mucoid background.

Physical exam revealed erythematous, indurated nodules on the right anterior and posterior lower leg. The patient had 3+ nonpitting edema of bilateral lower legs and feet, and new onset of progressive swelling of bilateral hands. The great toes were markedly enlarged, with overlying scarring at surgical incision sites (Figure 1).

As the pain and discomfort of her great toes and lower extremities remained debilitating and refractory to all first- and second-line treatment options for pretibial myxedema, we formulated a novel treatment option involving injection of the enzyme hyaluronidase. Hyaluronidase degrades glycosaminoglycans (GAGs), which accumulate in the dermis of localized myxedema lesions.1 An intradermal allergy test was performed first, revealing no hypersensitivity to hyaluronidase. Initially, hyaluronidase (200 units/1.2 cc) mixed with triamcinolone acetate (Kenalog 10 mg/cc) was injected into the left great toe, while hyaluronidase (200 units/1.2 cc) with lidocaine 1% was injected into the right great toe for comparison. The regimen was administered as follows:

Left great toe: 0.15 cc (25 units) hyaluronidase + 0.15 cc triamcinolone acetate 10 mg/cc = 0.3 cc total mixed syringe in two evenly distributed aliquots with 30G needle (two on dorsal aspect) (Figure 3). Right great toe: 0.15 cc (25 units) hyaluronidase + 0.15 cc lidocaine 1% = 0.3 cc total mixed syringe in two evenly distributed aliquots with 30G needle (one on dorsal aspect and one on plantar aspect) (Figure 3).

At one-month follow-up, a slight decrease in swelling and discomfort was observed, with the right and left toes affected equally. At that time, a repeat dose of hyaluronidase with lidocaine was administered to bilateral halluces:

Right great toe: 0.15 cc (25 units) hyaluronidase + 0.15 cc lidocaine 2% = 0.3 cc total mixed syringe in three evenly distributed aliquots with 30G needle (two on dorsal aspect and one on plantar aspect).

**Figure 1. Prior to treatment, bilateral great toe enlargement and scars from prior surgical incisions.**

**Figure 2. Punch biopsy of right lower leg showing abundant mucin within the reticular dermis, consistent with pretibial myxedema.**

**Figure 3.** Pretibial myxedema resulting in progressively worsening cutaneous induration and expanding nodules can lead to pain, discomfort and functional impairment. Treatment of resistant lesions presents a special challenge whereby topical therapies are insufficient, and systemic therapies are met with poor tolerability, low rate of effectiveness and the added risk of side effects. We report a patient with resistant pretibial myxedema nodules who demonstrated marked overall improvement of great toe lesions, including nodule size and associated discomfort, with repeat injections of hyaluronidase (Vitrase) both with and without triamcinolone acetate.
Two weeks post-procedure, there was again only a slight decrease in swelling, subjective discomfort, and impact on quality of life. Therefore, we increased the volume of hyaluronidase, added triamcinolone acetate 40 mg/cc, and increased the frequency of injections to every two weeks. At that time, we administered:

**Left great toe:** 0.30 cc (50 units) hyaluronidase + 0.30 cc triamcinolone acetate 40 mg/cc + 0.60 cc normal saline

**Right great toe:** 0.30 cc (50 units) hyaluronidase + 0.30 cc triamcinolone acetate 40 mg/cc + 0.60 cc normal saline

At two-week follow-up, the patient demonstrated a marked decrease in great toe pain, discomfort and size (Figure 4). The patient further reported substantial improvement in quality of life, including comfort while wearing shoes and overall satisfaction. Throughout the course of treatment, our patient did not report any significant adverse effects, noting only discomfort during injections, as well as slight injection site soreness lasting two to three days post-procedure. The patient will be continued on this most recent regimen of injections every two weeks, for maintenance and tight control of her symptoms. The patient is also being considered for adjunctive rituximab with IVIG therapy due to persistently elevated TSI levels and diffuse edema of dorsal feet and hands.

### Discussion

Localized or pretibial myxedema is characterized by cutaneous induration of skin due to mucin deposition in the dermis. Localized myxedema is also known as "dermatomy of Graves' disease" or "thyrdomatous" because it is often a sign of Graves' disease. Localized myxedema commonly occurs on the lower extremities due to their dependent position and subjection to mechanical stress. Furthermore, the first sign of disease frequently involves the hallux secondary to trauma caused by shoes. Rarely, myxedema can involve the face, upper extremities, lower abdomen and sites with traumatic history.

Diffuse non-pitting edema is seen due to dermal mucin retaining fluid, which can eventually evolve into elephantiasis. The lesions may be asymptomatic and primarily of cosmetic concern. However, quality of life is affected when edema and myxedematous lesions enlarge to create difficulty and pain while walking and wearing shoes.

Mucin is a component of dermal extracellular matrix located in the dermis and subcutaneous tissue. Normally, mucin is produced in small amounts by fibroblasts and is composed largely of GAGs. GAGs include those attached to a protein core, such as dermatan sulfate and chondroitin sulfate, and those without attachments, as in hyaluronic acid (HA).

First-line treatment includes high-potency topical corticosteroids with occlusion, intralesional corticosteroids, and compression stockings. The role of steroids is to improve symptoms and relieve pruritus. For refractory disease, second-line treatment includes pentoxifylline. Pentoxifylline is an analog of methylxanthine theobromine, which inhibits proliferation of fibroblasts and GAG synthesis.

As our patient failed treatment with corticosteroids, and was unable to tolerate pentoxifylline, we proposed injecting hyaluronidase, a naturally occurring enzyme that degrades HA and to some extent chondroitin and chondroitin sulfates. Hyaluronidase works by cleaving beta-1,4 glycosidic bond between C1 (N-acetylgulcosamine) and C4 (glucuronic acid).

In English literature, there are three manuscripts discussing the use of hyaluronidase to treat localized myxedema. All of the reports were in the wake of discovering the contents of myxedema lesions. In 1948, Melvin L. Grais presented a patient with pretibial myxedema lesions refractory to thyroid extract and propylthiouracil that were cosmetically displeasing. Hyaluronidase in increasing concentrations, mixed with saline, was injected into myxedematous plaques. The lesions decreased markedly in size and resolved without scar. However, this patient developed local injection site reactions, including erythema and edema. At high concentration, the patient developed systemic signs including fever and chills, which resolved within 48 hours. There is a disclosure in the article that the labeled strength of hyaluronidase preparation is not an accurate index of actual hyaluronidase activity at the time of use and that the authors cannot conclude the exact dose injected per treatment.

In 1949, Bloom et al. reported two cases of myxedematous lesions injected with hyaluronidase and normal saline. Both cases resulted in flattening of lesions without any adverse reactions. One of the case’s injections were discontinued after only a few weeks because the lesions became firm and resisted any injection of fluid. Donald Rosman in 1950 employed hyaluronidase injections in higher concentrations than previously reported plus normal saline, and subsequently applied pressure dressings to the lesions. Lesions resolved in both patients, with only erythema and occasional pain during injections reported as adverse events. Lesions injected only with normal saline did not improve. Upon discontinuation, lesions recurred; however, this is expected, since hyaluronidase is a palliative treatment directed toward a manifestation of the disease.

We used Vitrase, a commercially available hyaluronidase of ovine testicular origin. Vitrase is indicated to increase absorption of other drugs, increase tissue permeability to facilitate subcutaneous hydration and improve resorption of radiopaque agents. Off-label, it is used to treat vitreous hemorrhage and for reversal of hyaluronic acid filler. Reported adverse effects include, most commonly, local injection site reactions, and rarely (< 0.1%) allergic reactions. Our theory is that commercial hyaluronidase at regulated concentrations will break down the mucin and increase drainage of the excess GAGs, as well as facilitate absorption and effectiveness of concomitant triamcinolone acetate. Based on this mechanism of action, we expect that twice-monthly injections of hyaluronidase with triamcinolone acetate will ultimately continue decreasing the size of our patient’s lesions and provide remarkable symptomatic relief. To date, repeat courses of hyaluronidase both with and without triamcinolone acetate injections have been performed, and have resulted in significant overall improvement of cosmesis, lesional size, and associated pain and discomfort.

### Conclusion

Pretibial myxedema can affect a patient’s quality of life when lesions are of cosmetic concern, cause pain and/or result in difficulty ambulating, as seen in our case presentation. We have provided another successful treatment option, intralesional hyaluronidase with or without triamcinolone, that should be considered when lesions are refractory to first-line treatment options, such as topical and intralesional corticosteroids. Hyaluronidase injections decrease size and improve appearance of lesions, resulting in improvement of debilitating symptoms.
References


Neutrophilic Eccrine Hidradenitis: An Unusual Case and a Review of the Literature

Leslie Mills, DO,* Christina Steinmetz-Rodriguez, DO,** Alecia Folkes, DO,*** Robin Shecter, DO, FAOCD****

*Dermatology Resident, 2nd year, JFK Medical Center North Campus/Palm Beach Consortium for Graduate Medical Education, West Palm Beach, FL
**Dermatology Resident, 3rd year, JFK Medical Center North Campus/Palm Beach Consortium for Graduate Medical Education, West Palm Beach, FL
***Traditional Rotating Intern, LECOMT/St. John's Episcopal Hospital, Far Rockaway, NY
****Program Director, JFK Medical Center North Campus/Palm Beach Consortium for Graduate Medical Education, West Palm Beach, FL

Disclosures: None
Correspondence: Leslie Mills, DO; mills.leslie2012@gmail.com

Abstract

Neutrophilic eccrine hidradenitis (NEH) is a neutrophilic dermatosis primarily affecting the eccrine sweat glands in adult patients receiving chemotherapy, notably cytarabine for acute myeloid leukemia (AML). NEH is characterized by fever and erythematous papules and plaques resolving within one to two weeks of discontinuation of the offending drug. NEH has rarely been reported to occur in other malignancies, infections, or drug reactions, or in otherwise healthy children. We present a rare case of Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) complicated by NEH in a child receiving intensification chemotherapy with cytarabine, methotrexate, and dasatinib. The patient’s polymorphous eruption persisted for months despite discontinuation of the offending agents. We also discuss the pathogenesis, characteristics, and treatment of NEH.

Introduction

Neutrophilic eccrine hidradenitis (NEH) is an uncommon neutrophilic dermatosis of the eccrine sweat glands first described in 1982 by Harrist et al.1 NEH was initially described as a distinct disorder most often reported in adult patients receiving chemotherapy for malignancy, notably cytarabine induction chemotherapy for acute myeloid leukemia (AML), characterized by the onset of fever with erythematous papules and plaques resolving within one to two weeks of discontinuation of the offending agent.2 To date, cytarabine remains the most frequently reported cause of NEH. However, NEH has since been described in association with other malignancies, as a paraneoplastic syndrome or complication of infection, and following the ingestion of related immunomodulators or acetaminophen.3

We present a rare case of Philadelphia-chromosome positive acute lymphoblastic leukemia (Ph+ ALL) complicated by NEH in a child receiving intensification chemotherapy with cytarabine, methotrexate, and dasatinib, characterized by fever and a polymorphous eruption persisting for months despite discontinuation of offending agents. The findings are important in distinguishing NEH from mimics such as Sweet’s syndrome or other neutrophilic dermatoses, drug eruptions, infection, and leukemia cutis.

Case Presentation

An 8-year-old Hispanic male with Ph+ ALL presented to the emergency department with a two-day history of fever and rash on the extensor arms that spread to involve the cheeks, lower trunk, and legs. Dermatology was consulted to evaluate for Henoch-Schönlein purpura. The patient had been administered high-dose methotrexate and cytarabine 48 hours prior to initial presentation, and leucovorin two to three hours prior to initial presentation. He denied any associated pain, pruritus, burning, or bleeding, but admitted to tenderness on the lower lip. Review of systems was otherwise negative. Additional history included sulfa-induced urticarial eruption, seizure disorder, recurrent pneumonia and otitis media, asthma, and anemia requiring multiple transfusions. Home medications included dasatinib, levetiracetam, and acetaminophen. Family history was noncontributory. There were no sick contacts, travel, or exposure to animals or UV radiation.

Physical examination revealed non-tender, blanchable, edematous, erythematous, follicular papules and nodules, some with central dusky coloration, coalescing into plaques primarily on the extensor arms, lower back, buttocks, anterolateral thighs, and lateral lower legs in a symmetric distribution (Figures 1-4). Subtle, pinpoint, skin-colored to erythematous follicular papules and papular pustules, with variable perifollicular erythema, were noted on the cheeks, extensor arms, and abdomen (Figure 5). Additional findings included superficial erosions with hemorrhagic crusting of the lower lip with smooth erythema of the dorsal aspect of the tongue. As expected, pallor and diffuse alopecia were prominent. Palms, soles, and nails were spared, and there was no appreciable palpable lymphadenopathy. Our differential diagnosis included drug reaction, viral exanthems and other disseminated infections, erythema multiforme, Sweet’s syndrome, and leukemia cutis.
Histologic examination of punch biopsies of lesions on the extensor arm and thigh revealed focal hyperkeratosis, cleaving below the granular layer, and vacuolar interface dermatitis with scattered perivascular neutrophils and dyskeratotic cells within the eccrine sweat gland coils, most consistent with a drug reaction (Figures 6, 7). Follicular plugging was an incidental finding. Tissue cultures were negative. DIF was negative.

Routine laboratory tests included complete blood count (CBC) and complete metabolic panel (CMP), which revealed leukopenia with neutropenia, absolute neutrophil count (ANC) of 325/mm³, lymphocytosis, mild normocytosis, macrocytic anemia, thrombocytopenia, elevated transaminases, hypoproteinemia, and hypoalbuminemia. Renal function and coagulation profile were within normal limits. Serologic tests were negative for antistreptolysin O, human immunodeficiency virus (HIV)-1 and -2, hepatitis B virus (HBV), hepatitis C virus (HCV), mycoplasma pneumoniae IgM, parvovirus B19 (except for IgG), and Epstein-Barr virus (except for viral capsid IgG).

Polymerase chain reaction (PCR) targeting DNA of parvovirus B19, adenovirus, cytomegalovirus (CMV), human herpes virus (HHV)-6/-7, and herpes simplex virus (HSV)-1 and -2, together with RNA of enterovirus, were negative. Cultures taken from blood, including port line, throat, urine, lower lip, and cerebral spinal fluid (CSF), were negative. C-reactive protein (CRP) was only mildly elevated. Chest radiograph was normal. Bone marrow aspiration revealed minimal residual disease with major medical response, cellular marrow with erythroid and granulocytic hyperplasia.

Clinical and histologic findings were consistent with NEH, likely the result of cytarabine, although methotrexate could not be excluded as the offending agent. Further, dasatinib has been reported to cause follicular papular and pustular eruptions, similar to the acniform or keratosis pilaris-like eruption of our patient, with follicular plugging noted on histology as well.

Infectious disease was consulted by the pediatric hospitalist for empiric cephalaxin and micafungin, rather than fluconazole due to possible drug interaction with dasatinib, pending negative cultures. Due to the severity of the eruption, topical class I corticosteroid was incorporated into the regimen.

The patient was discharged when cultures were negative and he had been afebrile for 24 hours, with instructions to follow up with outpatient Dermatology. One month later, he presented to our dermatology clinic with only mild improvement of the lesions and was started on oral prednisolone with instructions to return in two weeks for re-evaluation.

Discussion

Neutrophilic eccrine hidradenitis (NEH) is an uncommon neutrophilic dermatosis primarily directed against the eccrine sweat glands. First described in 1982, the exact etiology is unknown, although NEH tends to occur in patients receiving cytarabine, as a complication of chemotherapy for acute myeloid leukemia (AML). Since then, other agents have been implicated, including bleomycin, methotrexate, anthracyclines, 5-fluorouracil, taxanes, cyclophosphamide, vinca alkaloids, and imatinib mesylate. In patients with chemotherapy-induced neutropenia, neutrophils may be absent from biopsy specimens, hence the suggested name “chemotherapy-induced eccrine hidradenitis.” NEH has also been reported after zidovudine treatment in HIV patients. Granulocyte-colony stimulating factor (G-CSF) and acetaminophen also may induce lesions of NEH. Clinically, NEH usually presents with erythematous papules and plaques, and less frequently as a polymorphous eruption of erythematous papules, small nodules, plaques, pustules, purpura, and urticaria. Areas most commonly include the face, trunk, and extremities. NEH presenting in the periorbital region of the face may mimic or orbital cellulitis. Lesions may be asymptomatic or tender. Fever often accompanies the cutaneous eruption, as seen in our patient. Because of these highly variable clinical presentations, it can be difficult to differentiate NEH from other neutrophilic dermatoses such as Sweet’s syndrome and pyoderma gangrenosum, which may also be associated with leukemia.

When NEH is drug-induced, most commonly a result of chemotherapy agents, it takes an average of 9.7 days for cutaneous signs and symptoms to appear following initial drug exposure. However, some cases have reported NEH in patients with no previous treatment. Previous studies have also shown an association of NEH with other hematological malignancies, Behçet disease, hemodialysis, and solid tumors such as osteosarcoma. Infectious causes include HIV, Streptococcus, Serratia, Nocardia, Enterobacter, and Staphylococcus aureus. Historically, NEH has been a condition most often affecting adults, and children with NEH have presented with lesions limited to the palms and soles, referred to as palmoplantar eccrine hidradenitis, an idiopathic variant of NEH. In contrast to NEH, palmoplantar eccrine hidradenitis is not associated with underlying disease, but is thought to occur as the result of mechanical and/or thermal trauma in otherwise healthy children. Regardless of etiology, the eccrine glands and coils serve as the ultimate target of destruction.

The pathophysiology of NEH is poorly understood. It is postulated that NEH is the result of a direct drug-induced effect mediated by neutrophilic chemotaxis. In this view, neutrophils are attracted to the site by cytokines C5a, interleukin-8, tumor necrosis factor alpha, and granulocyte colony-stimulating factor. Induction of an inflammatory response leads to cellular damage and eventual necrosis of the eccrine epithelium. Toxic byproducts of cytarabine may play a role in altering vessel walls, leading to leukocytoclastic vasculitis, which may also be seen in association with NEH. Alternatively, NEH has been placed on the neutrophilic dermatoses spectrum, seen as a paraneoplastic condition similar to Sweet’s syndrome. Also, NEH has been reported in healthy individuals, suggesting the possibility of underlying sweat gland abnormalities.

Diagnosis is confirmed by skin biopsy. Histologically, NEH usually demonstrates a perivascular and periductal infiltration of neutrophils around and within the eccrine glands. The upper dermis commonly shows edema and extravasation of red blood cells. Necrosis of the eccrine coils and glands may result from the neutrophilic inflammatory infiltrate. Infection as the cause of NEH must be excluded by tissue culture to avoid unnecessary use of antibiotics or changes in chemotherapy regimens.

NEH tends to be a self-limited disease, although some cases indicate the possibility of relapse upon future exposure to the same or a different chemotherapy agent. Topical or systemic corticosteroids may aid in the healing of skin lesions, as seen in our patient. Analgesics may be used for painful lesions. Of note, initiating dapsone prior to the administration of chemotherapy and continued daily for 14 days has been reported to help prevent relapse of NEH.

Conclusion

NEH is an uncommon neutrophilic dermatosis affecting the eccrine glands, most often seen in adults receiving chemotherapy for AML. In contrast, our patient was a child with Ph+ ALL, an extremely rare malignancy seen in children. Drug eruptions are often polymorphous and may have the potential to be life threatening, so clinicians must broaden their differential diagnosis to include other neutrophilic dermatoses or opportunistic infections with systemic features that mimic NEH. Our case emphasizes the fact that NEH can mimic many cutaneous eruptions, and biopsy is key in making a definitive diagnosis. NEH should be considered in the diagnosis of any eruption presenting with erythematous papules and plaques associated with fever, especially in the setting of chemotherapy.
References


Abstract

Morphea, also known as localized scleroderma, is a rare, fibrosing skin disorder caused by the dysregulation of collagen production. We report a 10-year-old girl with a history of morphea since age 4, with plaques involving multiple body sites and some lesions overlying joints. Our treatment plan involved oral methotrexate and topical tacrolimus ointment, which we believe halted progression of the disease. In this report, we review current treatment options and emphasize appropriate management of morphea in the pediatric population.

Introduction

Morphea is a rare, fibrosing skin disorder with disabling potential when affecting areas overlying joints. It is very important to start treatment as early as possible, especially in the pediatric population. There are only a few randomized placebo-controlled studies analyzing the efficacy of methotrexate (MTX) in the treatment of morphea. However, therapies with the greatest evidence for efficacy include MTX and/or systemic corticosteroids. We present a case of a 10-year-old girl with a six-year history of morphea involving multiple body sites and overlying joints, treated with MTX and topical tacrolimus ointment. This report also reviews current treatment options in the management of pediatric morphea.

Case Report

A 10-year-old Hispanic female presented to our clinic with a six-year history of asymptomatic, dry, dyspigmented plaques involving multiple body sites, with marked size discrepancy between her left and right forearms and hands. Patient work-up for autoimmune disease previously completed in Puerto Rico included normal chest X-ray, electrocardiogram, echocardiogram, and retinal examination, with no evidence of systemic involvement. Laboratory findings included CBC and CMP within normal limits; positive anti-nuclear antibody (ANA), 1:1280 homogenous pattern; and positive anti-double stranded DNA (anti-dsDNA), 1:640. The patient was treated with 15 sessions of narrowband UVB (NBVU) phototherapy, with no improvement of lesions. She was unable to continue phototherapy at the time due to insurance issues.

Reportedly, the lesions had been stable for two years prior to presentation. Clinical examination revealed firm, non-tender, atrophic white plaques with brown hyperpigmented borders affecting the left chest, mid-back, forearm, wrist and dorsal hand, and the right anterior shin and dorsal foot, with cutaneous induration of the right lower extremity evident (Figures 1a-d). The left forearm and hand were noted to be significantly smaller than the right, with tapering of digits and absence of nail-fold capillary changes (Figure 1a). On examination, the patient demonstrated normal joint mobility, full range of motion and muscle strength, and normal mouth-opening aperture. She denied Raynaud’s phenomenon, dysphagia, arthralgia, myalgia, headache, or history of seizures.

Laboratory work-up for systemic scleroderma included CBC, CMP, ANA, anti-topoisomerase I (Scl-70) antibody, anti-dsDNA antibody, anti-histone antibody, and procollagen type I intact N-terminal propeptide (PINP). Results revealed negative Scl-70 antibody (< 1.0 AI) and anti-dsDNA (2 IU/mL), while ANA was positive (1:160, homogenous pattern) and anti-histone antibody (4.2 U) and PINP (610 mcg/L) were highly elevated. Two punch biopsies were performed of lesions from the right lower extremity and left forearm. Biopsies showed findings consistent with morphea on histopathologic examination (Figure 2).

The patient was started on clobetasol 0.05% cream applied to affected areas twice daily but responded with minimal softening of lesions. Due to the potential disability involved with lesions overlying joints, we began this patient on methotrexate (MTX) 10 mg weekly with monthly lab monitoring; folic acid 1 mg daily, except on the day of MTX administration; and tacrolimus 0.03% ointment applied to affected skin daily. As of this report, the patient has had no complaints of side effects since starting MTX. Clinically,
lesions are softer to palpation and lighter in color. She continues to have full range of motion of all affected joints.

Discussion
Morphea is a rare, fibrosing skin disorder caused by the overproduction of collagen by fibroblasts, resulting in a thickening of the dermis, subcutaneous tissue, underlying bone, and rarely the central nervous system when present on the face and head.1,2 According to epidemiologic studies, disease incidence is estimated as 0.4 to 2.7 per 100,000 individuals, with a female-to-male ratio of 2 to 3:1 and equal prevalence in adults and children.3 A reported 90% of affected children present with morphea between 2 years and 14 years of age. Morphea is clinically differentiated from systemic scleroderma based on the absence of sclerodactyly, Raynaud’s phenomenon, telangiectasias, gastrointestinal involvement, and nail-fold capillary changes.1,2 Morphea has been associated with other connective tissue disorders, such as systemic lupus erythematosus, rheumatoid arthritis, Sjögren’s syndrome, juvenile dermatomyositis, polyosomatis, and eosinophilic fascitis, as part of an overlap syndrome.1

The morphea classification scheme is based on clinical criteria and includes five variants: circumscribed, linear, generalized, pansclerotic, and mixed.1,3 Linear morphea is the most common manifestation in pediatric populations, affecting 41.8% to 67% of children studied. It is characterized by linear induration involving dermis and subcutaneous tissue, which can be complicated by muscle atrophy, limb length discrepancies, and joint and bone deformity.2,4 Generalized morphea is a rare variant, occurring in 7% to 9% of morphea patients, that is typically limited to the dermis and defined by four or more plaques larger than 3 cm affecting at least two of seven anatomic sites (head-neck, each extremity, anterior trunk, posterior trunk). Generalized morphea patients commonly are detected to have positive autoantibodies, particularly ANA, on autoimmune serology testing.2 Our patient fits the criteria for mixed morphea, defined as two or more variants and occurring in 15% of morphea patients, as her clinical picture is consistent with both linear and generalized morphea phenotypes.1,4

The pathogenesis of morphea is poorly understood but postulated to be multifactorial, including genetic, autoimmune, and environmental factors leading to microvascular injury, stimulating an imbalance between collagen production and degradation.2 Triggers such as mechanical trauma at lesional sites, suggesting koebnerizing phenomena or infection with *Borrelia* spp., particularly European strains, have been described in the literature.2,4 Morphea patients commonly have positive auto-antibodies, with a high prevalence of positive ANA titers, homogenous pattern; single-stranded antibody; anti-histone antibodies; anti-topoisomerase II alpha antibody; and rheumatoid factor.2

Excess collagen deposition is thought to be activated by vascular injury via factors previously described.3,5 In the vascular theory, endothelial injury causes a release of inflammatory cytokines and subsequent up-regulation of the expression of adhesion molecules and E-selectins. This up-regulation recruits T-cells that produce pro-fibrotic cytokines, mainly interleukin 4 (IL-4), interleukin 6 (IL-6), and transforming growth factor-beta (TGF-β), leading to increased collagen production and extracellular matrix deposition favoring a type 2 helper T-cell response. TGF-β also decreases protease production, primarily through inhibition of matrix metalloproteinases, and increases protease inhibitors, causing an imbalance of collagen production and breakdown, thus favoring fibrosis and a resultant hardening of the skin.

The diagnosis of morphea is based on clinical features. Lesions initially present as erythematous to violaceous hyperpigmented patches or plaques, which evolve to become white and sclerotic centrally with a characteristic hyperpigmented border.2 Older, non-active lesions are white sclerotic plaques that may present with post-inflammatory hyperpigmentation. Biopsy is confirmatory of cutaneous disease and should be obtained prior to initiating systemic treatment in children, if indicated. Biopsy also allows for the histopathological delineation of early versus late disease-stage process; morphea is more responsive to therapy in the early stage, while disease is active. Furthermore, biopsy can be used to differentiate morphea from other sclerotic diseases such as lichen sclerosis et atrophicus, in which systemic therapy would not be appropriate.

Morphea treatment is guided by clinical findings, which are most predictive of individual disease course and severity.2 Suggested treatment algorithms are based on morphea subtype.4 Evidence-based treatment options are limited due to morphea’s relative rarity, making it difficult to perform large, randomized controlled trials. Completed randomized controlled trials in 2006 and 2009 indicate narrowband ultraviolet B light (NBUVB) phototherapy and topical 0.1% tacrolimus under occlusion, respectively, as safe and efficacious treatment options for morphea. Small prospective and retrospective studies also indicate calcipotriol in combination with betamethasone dipropionate, imiquimod, D-penicillamine, mycophenolate mofetil, cyclosporine, and photopheresis to be effective in treating children with morphea.6

Some children with morphea receive suboptimal therapy due to prescribing differences based on physician specialty as well as prescribing patterns that vary by age of disease onset.2 Studies indicate that general dermatologists are less likely to prescribe systemic immunosuppressives to children, while rheumatologists are more aggressive in their treatment and often prescribe systemic immunosuppressives. For best-practice disease management, general dermatologists may consider referral to a pediatric dermatologist when children present with severe morphea subtypes, particularly linear, as systemic immunosuppressive therapy is indicated.1,5 Similarly, phototherapy, which is an effective therapeutic option for morphea subtypes, is almost exclusively used by dermatologists and underutilized in other disciplines.6 Thus, morphea patients would benefit from comparative effectiveness studies and a multidisciplinary approach in developing treatment guidelines to be utilized uniformly across specialties.6

Determining the most appropriate treatment modality is complex and requires consideration of morphea subtype, disease extent and progression, and existing or potential physical deformity that can impede function. Determining phototherapy modality should also be based on these disease aspects in conjunction with study-based evidence and principles of phototherapy. Few published studies offer results reached by randomized trials or use of validated clinical score measurements, such as modified skin score (MSS) and ultrasound-measured dermal thickness.2

Phototherapy modalities utilized for morphea include psoralen UVA (PUVA), extracorporeal phototherapy, UVA-1, broadband UVA (BB-UVA), and NBUVB. Level 1 evidence supports BB-UVA, UVA-1, and NBUVB as therapeutic options for morphea, while extracorporeal phototherapy and PUVA bath/cream are supported by level 2 evidence.2 Randomized comparison trials indicate medium dose (50 J/cm²) UVA-1 is more effective than NBUVB in treating morphea as determined by the MSS; however, no significant difference was determined between low-dose (20 J/cm²) UVA and NBUVB.5 Studies comparing UVA-1 doses indicate variability in treatment efficacy. Thus, an optimum UVA-1 treatment dose still needs to be elucidated.7

Principles of phototherapy proven in numerous studies indicate UVA (higher wavelength) penetrates deeper into the dermis than NBUVB (lower wavelength). The concept of selecting phototherapy modality based on extent of dermal involvement and depth of wavelength penetration has been previously demonstrated in psoriasis and cutaneous T-cell lymphoma studies.2 Thus, by similarly applying this principle, morphea extending to deeper cutaneous tissue would respond best to BB-UVA/UVA-1 as opposed to NBUVB, which is more appropriate for treating early, superficial lesions. The average length of phototherapy treatment by which disease improvement can be appreciated is between 10 weeks and 20 weeks. A clear benefit of phototherapy is the ability to effectively treat individuals with widespread disease. However, patients with morphea extending into the subcutaneous tissue, fascia, or muscle are...
Systemic therapy with agents like MTX, mycophenolate mofetil, D-penicillamine, and cyclosporine should be highly considered in children with progressive or extensive cutaneous disease with lesions affecting the face or overlying joints, increasing the risk of developing both physical deformity and functional impairment. Children with severe morphea subtypes or children who exhibit progressive disease and have failed topical or phototherapy treatments would benefit from referral to a pediatric dermatologist for systemic management. D-penicillamine in combination with systemic corticosteroids was once considered the treatment of choice for severe morphea variants such as linear or generalized morphea in the pediatric population. Since 2000, systemic therapy with MTX in combination with systemic corticosteroids has become the first-line therapeutic option. In a retrospective study of 136 pediatric patients with morphea, MTX was prescribed to 39 patients at an initial dosage of 0.3 mg/kg/wk to 0.5 mg/kg/wk with folic acid 1 mg/day except on the day of MTX administration. MTX improved lesions in all patients except for one patient with morphea profunda and three patients with progressive hemifacial atrophy. Adverse effects of MTX were limited to gastrointestinal discomfort in five patients and increased hepatic transaminase in one patient.

Zulian et al. studied the long-term therapeutic role of MTX. The prospective study followed children with linear, generalized, and mixed morphea subtypes previously enrolled in a double-blind, randomized controlled trial. Patients were treated with oral MTX (15 mg/m²/wk) for at least 12 months and prednisone (1 mg/kg/d, with maximum dose of 50 mg) as a single morning dose for three months with gradual taper over one month compared to oral prednisone alone. The study also assessed clinical remission and complete remission as defined by therapeutic response maintained while on medication for at least six months and response maintained after stopping medication for at least six months, respectively. A cohort of 65 patients included 31 patients who responded to MTX at 12-month follow-up, 15 patients on MTX who relapsed but responded to a short course of oral prednisone in a previous double-blind study, and 19 patients assigned to placebo (oral prednisone alone) who relapsed but subsequently were started on MTX in an open-label study. Of the 65 enrolled patients, seven were lost to follow-up, while 48 (82.8%) responded to MTX; of those responders, 35 (72.9%) achieved complete clinical remission for 25.6 or more months after a mean of 27.5 months of MTX treatment. Zulian et al. determined oral MTX with concurrent prednisone administered in the first three months to be efficacious in treating children suffering from severe morphea. Furthermore, systemic treatment should be initiated early in disease onset, especially in linear, generalized, panniculotis, and mixed morphea subtypes. Additionally, MTX treatment for at least 24 months is recommended, as longer treatment duration may reduce the occurrence of relapse and incidence of disease flare following MTX tapering, a finding consistent with literature from Christen-Zaech et al.3,8

According to a 2013 article by Bielsa, psoralen UVA or NBUVB should be initiated in patients with generalized morphea without joint contractures, and if unresponsive following 40 sessions or eight weeks of phototherapy treatment, MTX combined with systemic corticosteroids can be administered. Patients with extensive cutaneous involvement, facial lesions, or lesions overlying joints should initially be treated with MTX combined with systemic corticosteroids, and patients who do not respond should then be started on mycophenolate mofetil. If still not responsive, phototherapy may be initiated.2,6,7,9 Patients with limited cutaneous involvement can be treated topically with tacrolimus, calcipotriene in combination with betamethasone dipropionate, or imiquimod.6

**Conclusion**

Few randomized placebo-controlled studies assessing the efficacy of MTX in morphea have been performed. However, therapies with the greatest evidence for efficacy include MTX and/or systemic corticosteroids, which are highly indicated for the treatment of progressive or linear, generalized, and mixed morphea subtypes in the pediatric population. Numerous retrospective studies indicate favorable response to MTX, with children exhibiting disease stabilization and often visible and palpable clinical improvement of skin lesions with minor adverse effects. Studies also support long-term maintenance MTX treatment for at least 24 months in children to best achieve prolonged and sustained disease remission.8 A multidisciplinary approach in performing comparative effectiveness studies is necessary to better develop morphea treatment guidelines and prevent morphea patients from receiving suboptimal therapy due to prescribing differences amongst specialists.6

**References**


A Rare Malignant Etiology of Zosteriform Lesions: Kaposi’s Sarcoma

Christina Steinmetz-Rodriguez, DO,* Leslie Mills, DO,** Robin Shecter, DO, FAOCD***

Abstract
Kaposi’s sarcoma, the most common neoplasm occurring in acquired immunodeficiency syndrome (AIDS), is a vascular tumor with often varied clinical presentation and a prevalence of 5% to 25% in the United States.1,2 We present the case of a 28-year-old man presenting with nodular, red-to-purplish macules in a zosteriform distribution, ultimately diagnosed as Kaposi’s sarcoma. Only three other cases of zosteriform Kaposi’s sarcoma have been reported in the literature. We review the classification, histology, and treatment modalities of Kaposi’s sarcomas as well as the differential diagnosis of cutaneous diseases that present in a dermatomal pattern.

Introduction
Kaposi’s sarcoma (KS) was first described in 1872 by the Hungarian dermatologist Moritz Kaposi as a pigmented, idiopathic sarcoma of the skin of elderly men. KS remains one of the most common malignancies in AIDS patients.1,2 Before the 1980s, KS was only described in elderly men of Eastern European, Mediterranean, or Jewish descent. KS emerged on a larger scale in the early 1980s in New York and San Francisco with the onset of the AIDS epidemic.2

Four variants of KS have been described in the literature: 1) the classic form, occurring in older men of Eastern European, Mediterranean, or Jewish descent. KS emerged on a larger scale in the early 1980s in New York and San Francisco with the onset of the AIDS epidemic.2

The etiology of this vascular neoplasm remained elusive until 1994, when Cheng et al. discovered a novel type of human herpesvirus in AIDS-associated KS lesions.3 The virus was found not only in nearly all KS lesions, but also in mice injected with the virus that later developed clinically and histologically KS-like skin lesions.3,4 This virus was later named human herpesvirus type 8 (HHV-8) and revolutionized our understanding of this neoplasm.

We describe a rare case of zosteriform KS in a 28-year-old man positive for human immunodeficiency virus (HIV) who presented with purplish papules in a dermatomal distribution associated with red-to-purple papules that had been present for three months. Four months prior to admission, the patient was hospitalized for appendicitis and underwent laparoscopic appendectomy. Postoperatively, he experienced thoracic dermatomal pain and developed eruptive, grouped vesicles above the hard palate. Faded purplish macules, 3 cm to 5 cm in diameter, were visualized above the medial malleolus and the medial thigh.

Case Presentation
A 28-year-old, HIV-positive Caucasian man presented to the emergency room with intractable superficial thoracic pain in a dermatomal distribution associated with red-to-purple papules that had been present for three months. Four months prior to admission, the patient was hospitalized for appendicitis and underwent laparoscopic appendectomy. Postoperatively, he experienced thoracic dermatomal pain and developed eruptive, grouped vesicles above the hard palate. Faded purplish macules, 3 cm to 5 cm in diameter, were visualized above the medial malleolus and the medial thigh.

Shave biopsy of a representative lesion revealed a dermal tumor (Figure 3, low magnification). Increased magnification revealed atypical pleomorphic spindle cells arranged in fascicles, with numerous extravasated erythrocytes and small capillaries between the collagen bundles (Figure 4). Numerous mitotic figures were present.
There are four subtypes of endemic KS: nodular, florid, infiltrative and lymphadenopathic. The nodular form presents similarly to classic KS and also demonstrates a good prognosis. The florid form is more aggressive, forming fungating and exophytic tumors. The infiltrative form involves invasion of the subcutaneous tissue and bone. Finally, the lymphadenopathic form, associated with a 100% fatality rate, is common in young Bantu children and presents with diffuse lymphadenopathy and visceral organ involvement. Treatment options include combination chemotherapy; however, in one report looking at three-year follow-up of patients with the florid or infiltrative type, only 14% remained disease-free, and 36% had died.

Iatrogenic KS presents in patients with severe immunosuppression resulting from organ transplant, autoimmune disease, or systemic immunosuppressive therapy for malignancy. Initially described in renal transplant patients, cases have also been reported in patients with pemphigus vulgaris, bullous pemphigoid, Wegener's granulomatosis, or systemic lupus erythematosus on immunosuppressive agents. The average time for development of lesions is 16 months after starting immunosuppressive therapy, and the lesions most often remain localized to the skin. About 30% of patients will die due to generalized KS, and tumor progression is correlated to degree of immunosuppression. Treatment options are difficult because the risk of death from organ rejection or autoimmune illness from discontinuing immunosuppressive therapy must be weighed against the risk of death from KS.

Finally, epidemic KS, which occurs in HIV-positive patients, has lesions that appear predominately on the face, neck and upper trunk, not the lower legs as in classic KS. Furthermore, the lesions appear as reddish-pink macules and papules, as clinically demonstrated in our patient, not the purplish macules seen in classical KS. Lesions on the oral mucosa, such as the hard and soft palates and genitalia, are not uncommon. Reports also note involvement of the lymph nodes and gastrointestinal tract as seen on endoscopy, with lesions present from the esophagus to the rectum and on the lungs, liver and spleen, as seen in our patient. Lesions evolve from faint and macular in the early patch stage to papules and plaques in the plaque stage, finally forming large, elevated nodules in the nodular stage. Systemic symptoms such as fever, chills, weight loss, diarrhea and fatigue often appear with the nodular stage. Treatment includes highly active antiretroviral therapy (HAART), intralesional therapy with vinblastine, radiation therapy and topical altretinoin. Systemic chemotherapy for extensive cutaneous lesions or visceral involvement includes doxorubicin or daunorubicin as first-line agents.

Zosteriform KS, as seen in our patient, is an extremely rare clinical manifestation of KS, with only three other cases reported in literature. Herpes zoster is the most common eruption to follow a dermatomal distribution, giving rise to the name zosteriform; however, other cutaneous lesions have been reported to occur in such a pattern, including papular lesions of...
lichen striatus, linear epidermal nevus, nevus comedonicus, verruca plana, lichen planus, lymphangioma circumscriptum, Hailey-Hailey disease, Darier disease, and syringoma (Table 2). Uncommonly, the skin can present as a site of metastasis, with an incidence of 2.5% to 5%, also in a dermatomic distribution. Lipoma, leiomyoma, blue rubber bleb nevus, vascular hamartoma, and granuloma annulare must be ruled out as well. Lesions reported as occurring at prior sites of herpes zoster include those of granuloma annulare, sarcoidosis, angiosarcoma, lymphoma and, in one case, KS. Zosteriform lesions of KS at sites of prior herpes zoster is hypothesized to occur via the Koebner phenomenon. Numerous accounts in the literature note the onset of KS lesions at sites of trauma such as horse bites, gnat bites, human bites, surgery and nail puncture wounds. Thus, in our patient, herpes infection might have resulted from decreased resistance in the dermatomes affected by the zoster, resulting in attraction of metastases to an area of traumatized skin. Other possible etiologies include spread via lymphatic and hematogenous routes or via the fenestrated vasculature of the dorsal root ganglion, perineural lymphatic invasion as seen in prostate cancer, and HHV-8 viral particles engrafted on SCID mice induces Kaposi’s sarcoma-like lesions. J Dermatol Sci. 2003 Jul;26(3):182-93.

Histology

Regardless of KS subtype, all lesions appear histologically identical on pathology. The histologic hallmark of KS is an admixture of spindle cells and slit-like vascular spaces. As lesions clinically progress through the patch, plaque and nodular stages, so does the histology of KS, with only three other reported cases in immunosuppressive treatment for granulomatosis with polyangiitis (Wegener’s). JAAD Case Rep. 2020 May;15(2):71-3.

Table 2. Differential diagnosis of papular dermatomal lesions

<table>
<thead>
<tr>
<th>Differential Diagnosis of Zosteriform Papular Lesions</th>
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<tr>
<td>Lichen striatus</td>
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<td>Epidermal nevi</td>
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<td>Basal cell nevus syndrome</td>
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<td>Nevus comedonicus</td>
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<tr>
<td>Verruca plana</td>
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<td>Lichen planus</td>
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<td>Hailey-Hailey disease</td>
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<td>Darier's disease</td>
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<td>Syringoma</td>
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<td>Becker’s nevus</td>
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<td>Connective tissue nevus</td>
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<td>Granuloma annulare</td>
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<td>Localized scleroderma</td>
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<td>Sarcoidosis</td>
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<td>Syphilis</td>
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<td>Cutaneous leishmanianiasis</td>
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<td>Angiokeratoma</td>
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<td>Lichen aureus</td>
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<td>Localized lymphangioma circumscriptum</td>
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<td>Psoriasis</td>
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<tr>
<td>Porokeratosis</td>
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<td>Malignancies: angiosarcoma, visceral and hematologic neoplasms</td>
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Table 3: Histologic Characteristics of KS

<table>
<thead>
<tr>
<th>Type</th>
<th>Histological Characteristics</th>
<th>Important Signs</th>
<th>Immunohistochemical Markers</th>
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<tbody>
<tr>
<td>Patch</td>
<td>Subtle thin-walled or jagged vascular spaces</td>
<td>Promontory sign</td>
<td>CD31+, CD34+, Factor VII RAg +, vimentin +, D2-40+, HHV-8</td>
</tr>
<tr>
<td>Plaque</td>
<td>Diffuse dermal vascular infiltrate with dissecting vascular channels</td>
<td>Autolumination, Promontory sign</td>
<td>CD31+</td>
</tr>
<tr>
<td>Nodular</td>
<td>Spindled cells arranged in fascicles</td>
<td>Autolumination</td>
<td>Desmin -</td>
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References


A Report of Amniotic Band Syndrome and Keratoderma with a Review of Constricting Band Syndromes

Luke Maxfield, DO,* Muneeb Shah,** Sarah Belden, DO,*** Jason Barr, DO****

*Transitional Year Intern, Sampson Regional Medical Center, Clinton, NC
**Medical Student, 3rd year, Nova Southeastern University College of Osteopathic Medicine, Clearwater, FL
***Dermatology Resident, 2nd year, Affiliated Dermatology/Midwestern University OPTI, Scottsdale, AZ
**** Surgical and Medical Dermatologist, Affiliated Dermatology/Midwestern University OPTI, Scottsdale, AZ

Disclosures: None
Correspondence: Luke Maxfield, DO; luke.maxfield@med.lecom.edu

Abstract
Amniotic bands are intrauterine fibrous cords that adhere to the growing fetus and cause mechanical trauma or vascular compromise. Associated defects range from hand creases to amputation, or even death in severe cases. We present a patient with a history of amniotic band syndrome with right leg amputation, constriction of the right fourth digit, and new-onset keratoderma involving the left plantar foot and bilateral palmar bands. This patient’s medical presentation emphasizes the importance of understanding the relationships between constricting band syndromes and palmoplantar keratoderma. We review previous literature documenting the association between amniotic band syndrome, pseudoainhum, and palmoplantar keratoderma.

Introduction
Although some authors have asserted that amniotic band lesions and pseudoainhum are distinct disease processes, pseudoainhum has been seen in patients with amniotic band syndrome. While both diseases involve constricting cutaneous lesions, their onset, causality, and relationships are dramatically different. We present a patient with a history of amniotic band syndrome with resulting right lower extremity amputation who presented to our clinic with new-onset keratoderma of the bilateral palms and left plantar foot. We also provide a literature review of palmoplantar keratodermas associated with amniotic band syndrome and pseudoainhum.

Case Presentation
A 26-year-old Caucasian female presented with roughening over the plantar portion of her left foot that had been progressing over the past several years. The patient had attempted to soften the area using foot soaks, a pumice stone, topical antifungals, and topical clotretasol over this same period, without noticeable relief. The patient denied any previous similar episodes. She also denied a family history of palmoplantar keratoderma or other cutaneous pathologies. Her medical history was positive for childhood eczema that had long since resolved, right lower extremity amputation, and a congenital constriction band deformity of the right fourth finger. She took no prescription medications but did take multivitamins. Physical exam showed focal hyperkeratotic plaques on the weight-bearing surface of the left foot with secondary fissuring (Figure 1). The hands were involved to a lesser degree, with thin scales over the left palm and digits bilaterally. The right hand showed a bulbous appearance of the fourth digit secondary to a focal constricting band distal to the interphalangeal joint (Figure 2). Differential diagnosis included acquired palmoplantar keratoderma with pseudoainhum, palmoplantar psoriasis, punctate palmoplantar keratoderma, irritated contact dermatitis, and atopic dermatitis. The patient was sent home with a working diagnosis of acquired palmoplantar keratoderma and was prescribed topical urea (40%) cream to apply to the foot BID at night with occlusion, and 10-minute bleach bath soaks two to three times per week. The patient failed to return for her next appointment, and despite repeated attempts to contact the patient, she was subsequently lost to follow-up.

Discussion
Constriction bands, which result in significant morbidity and mortality, are seen in amniotic band syndrome (ABS),1 ainhum, and pseudoainhum.2 ABS is thought to result from tears in the amnion that lead to fibrous adhesions to, and constrictions of, the developing fetus. The incidence is thought to be 1:10,000. Maternal risk factors for ABS include epidermolysis bullosa, connective tissue disorders, and prenatal abdominal trauma, such as amniocentesis. Ainhum, which is most prevalent in continental sub-Saharan Africa, is defined as idiopathic auto-amputation of a digit due to a constriction band. Pseudoainhum presents as a circumferential constriction band, usually around a digit, that has the potential to progress to auto-amputation. Unlike ainhum, pseudoainhum has no racial predilection.2 It has been described as secondary, sporadic, and a component of hereditary palmoplantar keratodermas, as well as in association with psoriasis.3,4 While many authors exclude cases of ABS auto-amputation from the pseudoainhum category,2 others use “pseudoainhum” and “ABS” interchangeably, with the rationale that the constriction bands are secondary to amniotic band syndrome.4,5

Theories on the pathogenesis of amniotic band syndrome are speculative and point to both intrinsic and extrinsic processes. The intrinsic theory states that deformities result from defective germ cells within the embryo. The extrinsic theory states that an early rupture of amnion results in decreased intra-amniotic fluid, which allows the mesoderm to contact the fetus, resulting in constricting bands.7

Theories on the pathogenesis of pseudoainhum are speculative and include infectious processes, fibrogenetic tendencies related to race, vascular abnormalities, and mechanical effects secondary to hyperkeratosis.3 Hyperkeratosis of the skin leads to formation of a circumferential groove around a digit. As the groove continues to deepen, the underlying vasculature becomes compromised, leading to a cessation of blood flow. The bone distal to the groove is eventually separated from the body, and auto-amputation occurs. Although the presentation of pseudoainhum does not always follow this pattern, hyperkeratosis is consistently present on histological exam.

Palmoplantar keratodermas (PPKs) appear clinically as abnormal thickening of the skin of the palms and soles.8 Hyperkeratosis is present on histological examination.3 PPKs can be inherited.
or occur sporadically and, in contrast to ABS, have often been seen in association with pseudoainhum and various inherited syndromes such as mal de Meleda and Vohwinkel syndrome. Mal de Meleda is an autosomal-recessive disease that appears early in life and is characterized by a triad of acral hyperkeratosis, malodorous hyperhidrosis, and nail abnormalities. Vohwinkel syndrome is an autosomal-dominant disease characterized by diffuse honeycombed palmoplantar keratoderma with associated sensorineural deafness, mental retardation, and alopecia. Vitamin A analogs, such as etretinate, have been shown to be effective in treating hereditary PPKs, as have urea-based topical formulations. Our patient's case does not fit into any of the known hereditary PPKs. The diagnosis of ABS is primarily clinical and does not routinely require workup beyond prenatal ultrasonography showing amniotic bands and restricted motion of the fetus. Similarly, in most instances, pseudoainhum is a clinical diagnosis. Plain radiograph of the affected digit should be performed to assess the integrity of the bone distal to the constricting band, as complete resorption of the digit has been observed in some cases. A thorough workup must be initiated to determine if the pseudoainhum is an isolated occurrence, part of a larger hereditary syndrome, or secondary to another disease process. A family history is necessary to rule out hereditary PPKs. In equivocal cases, a biopsy can be performed.

When pseudoainhum arises from psoriasis, treating the underlying psoriasis, with oral retinoids and topical corticosteroids, has led to resolution in some cases. A combination of a topical calcineurin-inhibitor and UVB phototherapy was successful in a single case. Other reports show success with surgical release of the fibrotic band under local anesthesia. Amputation can be considered when all other treatment modalities are exhausted, as auto-amputation is inevitable and can be painful in some cases.

Conclusion
In summary, our patient, with a previous history of ABS, presented with new-onset PPK. While the co-occurrence of these distinct pathologies is likely coincidental, this presentation provided an opportunity to review the existing literature on ABS and constriction band syndromes. Additionally, it prompted the investigation of a seldom-explored relationship between ABS and PPK. Unfortunately, our patient, with no personal or family history of constriction band lesions or PPK, was lost to follow-up and further in-depth workup that may have been beneficial, including histology and genetic testing.

References
A Review of Primary Cutaneous Amyloidosis

Jared Heaton, DO,* Natalie Steinhoff, DO,** Brian Wanner, BA,*** Michael Krutchik, DO****

*Dermatologist, Legacy Dermatology, Bountiful, UT
**Dermatology Resident, PGY-3, Nova Southeastern University College of Osteopathic Medicine, Largo Medical Center, Largo, FL
***Osteopathic Medical Student, OMS-IV, Des Moines University College of Osteopathic Medicine, Des Moines, IA
****Dermatologist and Clinical Faculty, Nova Southeastern University College of Osteopathic Medicine, Largo Medical Center, Largo, FL

Disclosures: None
Correspondence: Natalie Steinhoff, DO; NatalieSteinhoff@gmail.com

Abstract

Primary cutaneous amyloidosis is characterized by amyloid deposition in the skin without systemic involvement. This article reviews the three main variants of primary cutaneous amyloidosis, lichen, macular, and nodular, and briefly discusses rare forms.

Introduction

Primary cutaneous amyloidosis (PCA) is characterized by deposition of amyloid in the skin with no extracutaneous involvement. The three main variants are lichen, macular, and nodular amyloidosis. Of these, macular and lichen amyloidosis are most common. They are clinically distinguishable but have the same keratinocyte-derived amyloid K (AK) protein deposited in the papillary dermis, so they are often considered different manifestations of the same disease.1,2,3 Classically, macular amyloidosis presents on the upper back as poorly demarcated, hyperpigmented macules coalescing into pruritic patches and plaques. On the lower extremities, lichen amyloidosis is more often presents as discrete, hyperkeratotic papules forming larger plaques. Biphase amyloidosis occurs when macular and lichen variants present simultaneously and has been reported in 18.75% of PCA cases.2,4,11

The nodular variant is less common and involves dermal and subcutaneous deposition of amyloid light chain (AL). AL is derived from immunoglobulin light chain material created by infiltrating plasma cells. It is the only form of primary cutaneous amyloidosis in which the amyloid deposits are of the light chain subtype. This is the same subtype found in systemic amyloidosis associated with plasma cell dyscrasias and multiple myeloma. The nodular type is typically found on acral sites but can also appear on the face or trunk. It generally appears as single, or less commonly multiple, pink to tan, waxy papule or nodule that often hemorrhages with slight trauma.4 All three variants of PCA display apple-green birefringence under polarized light due to the β-pleated sheet structure of the amyloid protein.2

This article reviews the three main variants of PCA along with rarely reported types. The clinical and histological presentations and the diagnosis and treatment of PCA will be discussed.

Lichen and Macular Amyloidosis

PCA is seen most often in persons of South American, Middle Eastern or Asian ethnicities.2 Most cases are sporadic, although an autosomal-dominant family history is present in up to 10% of cases. PCA is rare in children, but familial forms commonly present during the second decade of life.4

Lichen amyloidosis is most common in persons of Chinese ancestry. It typically appears as red-brown, hyperkeratotic, pruritic papules on the shins, calves, ankles and dorsa of feet and thighs (Figure 1).4,6,9 Hyperkeratotic plaques may be present and often appear similar to plaques of lichen planus, lichen simplex or nodular prurigo.8 Cases of lichen amyloidosis limited to the anosacral region or the auricular concha have been documented in the literature.8

In macular amyloidosis, small, gray-brown macules may blend together to produce hyperpigmented patches. These hyperpigmented macules or patches are frequently found on the upper back and less commonly on the chest or extremities (Figure 2).10 Macular amyloidosis has been described as appearing similar to fading lichenoid inflammation, post-inflammatory hyperpigmentation, and the “dirty neck” of atopic eczema.8,11 Unusual variants have been described as periorcular hyperpigmentation, nevoid hyperpigmentation following Blaschko’s lines, and diffuse macular amyloidosis with an incontinentia pigmenti-like pattern.8,12

In both macular and lichen amyloidosis, chronic scratching in susceptible individuals is thought to contribute to the mechanism of amyloid deposition. The process of amyloid deposition involves filamentous degeneration and apoptosis of basal keratinocytes followed by conversion of filamentous masses (or colloid bodies) into amyloid material in the papillary dermis.1,8,11 That lichen and macular amyloidosis have similar amyloid deposition and can occur simultaneously supports the idea they are different manifestations of a common etiology.1,8,11,14 Also, new insight into amyloid diseases has shown the pathology is due not only to accumulation of fibrillar material but more so to the presence of smaller misfolded protein species, termed oligomers.25 Clos et al. proposes that oligomers are formed intracellularly in the basal layer and can either cause immediate cell death and amyloid formation or be released from the basal cells into the dermis. The oligomers are then consumed and accumulate in dermal macrophages and fibroblasts, giving rise to the amyloid aggregates seen in PCA.21,26

In addition to the characteristic features seen by the naked eye, Chuang et al. did a study on the dermoscopic features of 35 cases of PCA. The most common finding was a brown or white central hub surrounded by various patterns of pigmentation. Of the 18 cases of macular amyloidosis in the study, eleven patients showed white central hubs, four patients showed brown hubs, and three showed both.4 The 17 cases of lichen amyloidosis displayed whitish central hubs or whitish scar-like centers surrounded by brown dots or a white rim. Of the cases with whitish central hubs, half also had the whitish scar-like pattern for some lesions. This study helped demonstrate that dermoscopy may assist in achieving an accurate diagnosis of PCA, but more studies are needed to delineate the clinical usefulness of dermoscopy.

Figure 1. Hyperkeratotic, hyperpigmented papules and plaques on bilateral shins of a patient with lichen amyloidosis.

Figure 2. Hyperpigmented patch on the upper back of a patient with macular amyloidosis.

Figure 3. Histological features of amorphous, eosinophilic amyloid deposited in the dermis.
While the diagnosis of macular and lichen amyloidosis relies on clinical identification of characteristic skin findings, definitive diagnosis requires histological confirmation. On hematoxylin and eosin (H&E) stain, both macular and lichen amyloidoses demonstrate pink amyloid deposits in the papillary dermis (Figure 3). Histologies are similar as well, but lichen amyloidosis typically has more amyloid deposited. Lichen amyloidosis also commonly has secondary effects from rubbing, causing it to demonstrate irregular acanthosis, hypergranulosis, and hyperkeratosis of the epidermis, features similar to macular amyloidosis and lichen simplex chronicus. Other common features seen on H&E include pigment loss, fissuring of the amyloid deposits, and extravasation of red blood cells.

The amyloid may be seen with several stains, including methyl violet, crystal violet, thioflavin T and Congo red. Congo red is one of the most common staining techniques, as amyloid shows a characteristic apple green birefringence when viewed under polarized light. An H&E stain may give suspicion for amyloid diagnosis, but Congo-red staining under polarized light has proved sensitive and definitive. Vijaya et al. helped demonstrate the importance of Congo red in a study of 45 cases of suspected amyloidosis. The results showed that most patients tested positive for apple-green birefringence under polarized light. The labeling of cytokeratin (CK) 5 might also be useful in the diagnosis of both lichen and macular amyloidoses. Studies by Huigol et al. and Apaydin et al. suggest CK 5 might be involved as a common precursor in amyloid formation.

Numerous treatments for PCA aim to either relieve itch or remove amyloid deposits in the papillary dermis. Treatment of macular and lichen amyloidoses also involves reducing friction to the skin. Identifying the cause of rubbing, whether it be habit, pruritus, neuropathy, or a combination of these, may be of benefit. Therapies include topical or intralesional corticosteroids, capsaicin, topical lidocaine, topical calcineurin inhibitors (specifically 0.1% tacrolimus), calcipotriol, topical dimethyl sulfoxide, phototherapy (broadband and narrowband UVB, psoralen plus UVA photochemotherapy with oral actretin), oral retinoids (actretin), cyclosporine, pulsed dexamethasone-cyclophosphamide, acyclovir and interferon-alpha, dermatoblast, Nd-YAG laser, pulsed dye laser, CO2 laser and hydrocolloid dressings. The large array of treatment options demonstrates the difficulty in managing PCA.

Frolich et al. describe an interesting treatment option in a case of a 67-year-old Caucasian female with therapy-resistant pruritus in lichen amyloidosis on her upper back. After 26 years of pruritus, this patient responded to menthol with cool showers or cool packs, and when menthol is applied to the skin, a cooling sensation occurs due to menthol chemically triggering cold sensitive TRPM8 receptors in the skin. Studies have shown that menthol diffuses through the stratum corneum and increases drug diffusion and separation. Also, it has been demonstrated that menthol selectively activates K-opioid receptors, which may help explain its antipruritic effects.

Another new treatment option targets IL-31 and oncostatin M receptor b (OSMRb). Tanaka et al. discuss the involvement of these receptors in mechanisms of pruritus in familial PCA. Missense mutations have been identified in OSMRb, an interleukin (IL)-6 family cytokine receptor, and interleukin 31 receptor A (IL31RA) in patients with familial PCA. Tanaka et al. propose that signaling abnormalities from these receptors could lead to keratinocyte apoptosis, subsequent amyloid accumulation, and changes in the number of cutaneous nerves, leading to pruritus. Additional research is necessary to further understand and develop treatments aimed at these receptors.

Nodular Amyloidosis

Primary cutaneous nodular amyloidosis (PCNA) is very rare, with approximately 60 cases recorded in the medical literature up to 1994. In contrast to lichen and macular amyloidoses, nodular amyloidosis shows no prediction for certain ethnic groups. Recent studies indicate nodular amyloidosis occurs equally in both genders and most commonly impacts patients between 50 years and 60 years of age. It typically presents as single or, less commonly, multiple pink to yellowish brown, waxy nodules ranging from several millimeters to several centimeters in size. While a definitive cause of PCNA is unknown, it is understood that amyloid deposits in nodular amyloidosis originate from immunoglobulin light chains secreted by local plasma cells. The pathophysiology involves plasma-cell infiltration of the skin followed by monoclonal AL amyloid deposition in the dermis, subcutis, and around the blood vessels and nerve sheaths. The literature hypothesizes that PCNA is a form of plasma cell or plasma-cell dyscrasia.

PCNA nodules most often appear on the face, scalp, acral areas and genitalia. There are documented cases of nodular amyloidosis occurring in other areas of the body, however, such as the upper back and planter surface of the foot. PCNA lesions may resemble large bullae, and the epidermis may appear atrophic or anetodermic; the nodules may be quite friable, contain superficial telangiectasias, or hemorrhage as a result of perivascular amyloid deposition. Terushkin et al. report a case of amyloidosis involving AL amyloid that appeared bruise-like and was not nodular in nature. A histopathological diagnosis of PCNA was proposed for this lesion. PCNA has been associated with autoimmune connective-tissue disorders including primary biliary cirrhosis, systemic lupus erythematosus, Sjögren’s syndrome, systemic sclerosis, and rheumatoid arthritis. Sjögren’s syndrome is a chronic, lymphoproliferative autoimmune disease found in a significant number of PCNA cases. Results in a retrospective study by Meijer et al. supported PCNA with Sjögren’s syndrome as a distinct clinical entity. This was based on four interrelated factors, including the type of AL amyloid involved, the localized deposition of AL amyloid, the presence of light chain-restricted plasma cells near the amyloid deposits, and the relationship with Sjögren’s syndrome. Summers and Kendrick described a case of a 69-year-old woman with prior history of CREST (calcinosis, Raynaud phenomenon, esophageal motility disorders, sclerodactyly, and telangiectasia) syndrome, type 2 diabetes mellitus, and fatty liver, who presented with a brown papule on the left shin. The initial biopsy indicated macular and lichen amyloidosis with involvement of the papillary dermis. Over the next three years, more than 20 yellow, waxy nodules developed on her bilateral lower extremities, ranging in size from 1 cm to 4 cm. Biopsies stained positive for amyloid extending from the superficial papillary dermis to the subcutaneous tissue, results consistent with nodular amyloidosis. This is thought to be the first published case examining an association between PCNA and systemic sclerosis, including the CREST variant of limited cutaneous systemic sclerosis.

Traumatic injury to tissue is recognized as a triggering factor of PCNA in some cases. Dong Yoon Lee et al. described a tumefactive nodule consistent with PCNA on the scalp of a 50-year-old Korean man with a history of repeated head trauma from a soccer ball. Kalajan et al. described another patient who presented with a three-year history of a posttraumatic, slow-growing nodule on the chin caused by a thrown beer can. This nodule was consistent with PCNA and eventually began...
to enlarge and develop additional nodules. These articles demonstrate that trauma may be an inciting event for PCNA.

The diagnosis and differentiation of nodular amyloidosis is established via tissue biopsy, radiographic examination, and evaluation of immunoglobulins to detect latent paraproteinaemia and systemic disease. Since the amyloid fibrils are deposited from the dermis to subcutaneous tissue, as well as within blood vessel walls, biopsy specimens should include full-thickness skin into subcutaneous fat.

The amyloid chains involved in PCNA are indistinguishable from those deposited in the skin and other tissues in primary systemic amyloidosis.

Thorough work-up and close follow-up is recommended, since up to 7% of PCNA patients will eventually develop systemic involvement. It is also essential to exclude systemic involvement, because up to 40% of patients with primary systemic amyloidosis will present with identical cutaneous findings to those seen in PCNA.

Physical exam findings such as periocular purpura, macroscopias, carpal tunnel syndrome and nail dystrophy secondary to amyloid deposition all point to systemic involvement. Initial lab tests should include a CBC, CMP and urinalysis. A urine and serum protein electrophoresis should be ordered to rule out multiple myeloma and other monoclonal gammapathies. An electrocardiogram, echocardiogram and chest X-ray can provide further evidence of an infiltrative process in the heart and lungs. Biopsies of the abdominal fat pad, oral or rectal mucosa, liver, muscle, bone or transverse carpal ligament can be performed if clinical suspicion points to systemic involvement.

Paraproteinaemia in patients with PCNA may also indicate progression to systemic amyloidosis. Annual follow-up studies should be performed to monitor for progression. The advancement of PCNA to systemic amyloidosis, however, is uncommon, particularly if no clinical or laboratory evidence for systemic disease is present at the time of diagnosis.

Treatment of PCNA is individualized and based upon clinical presentation. Surgical removal, dermabrasion, carbon dioxide laser, pulsed dye laser, and destruction of the lesions by electrodessication and curettage have resulted in variable success.

Rare Variants of Primary Cutaneous Amyloidosis

Several cases of rare variants of PCA have been reported. Papular amyloidosis of the auricular concha was first reported in 1988 and is considered an uncommon variant. Four adult patients were described with newly formed papules of the auricle that coalesce into plaques. Histopathology of both studies demonstrated nodular deposits of amyloid in the papillary dermis. One study performed immunoperoxidase staining, which demonstrated positive antikeratin antibody EK1H4, confirming the keratinocyte origin of the amyloid.

Amyloidosis cutis dyschromica, another rare variant, was first described in a young female in 1970. In 2011, Garg et al. performed an extensive review of literature and detected only 20 case reports of amyloidosis cutis dyschromica worldwide. The disease is characterized by speckled reticular hyperpigmentation with hypopigmented macules vastly dispersed. Minimal or no itching may be present, and onset is usually before puberty. Histopathology demonstrated focal amyloid deposition in the papillary dermis. Genetic predisposition and environmental factors, particularly a large amount of sun exposure, have been proposed as the underlying cause.

Bullous amyloidosis is another rare form of PCA. The literature suggests 88% of bullous amyloidosis cases have systemic involvement. There may also be a genetic component, as one report notes a family in which eight members were affected within two generations. The lesions in this variant exhibit subepidermal blisters and are often described as being intermixed with hyperkeratotic papules of lichen amyloidosis. A case by Chandran et al., however, reported the bullae and erosions to be isolated. While the mechanism of bullae formation is unclear, it is believed that trauma or rubbing is the primary precipitating factor.

Uncommon presentations of diffuse macular amyloidosis include nevoid-like hyperpigmentation, widespread diffuse pigmentation, poikiloderma-like presentation, and an incontinentia pigmenti-like pattern. Wan et al. reported a case of unusually diffuse macular amyloidosis with an incontinentia pigmenti-like pattern in a 28-year-old woman. She presented with diffuse nonpuritic hyperpigmentation that followed Blaschko lines and had been present since early childhood. Skin biopsy confirmed amorphous deposits of eosinophilic material consistent with amyloidosis.

Another example, described by Chandran et al., involved a 27-year-old Chinese woman with primary localized cutaneous amyloidosis with lichen, poikiloderma-like, dyschromic and bullous variants. All of the subtypes occurred in isolation from one another, and no associations with systemic involvement were identified. Biopsies were taken from each distinct morphology, which included lichenoid papules on the shin, poikiloderma in the axilla, a blister on the knee, an erythematous annular plaque on the temple and a pigmented macule on the hip. All demonstrated the characteristic amyloid deposition found in PCA, stained positive for Congo red and showed apple-green birefringence under polarized light.

Discussion

As demonstrated in this review, PCA can have a wide range of clinical presentation. Hyperkeratotic pruritic papules on the shins that coalesce into plaques are characteristic of lichen PCA. Hyperpigmented pruritic macules on the upper back that coalesce into patches are characteristic of macular PCA. Biphasic amyloidosis involves lichen and macular PCA occurring simultaneously. Nodular PCA characteristically presents as single to multiple, tan to pink waxy nodules on acral areas of the body. Less-common variants have a wide array of presentations, including bullous, poikiloderma-like, dyschromic, incontinentia pigmenti-like, and nevoid-like patterns.

While lichen and macular PCA are the most common presentations, nodular and the uncommon variants of PCA should be included in a differential diagnosis for cases that present similarly to the ones mentioned in this review. Biopsy of the lesion and histological identification of amorphous eosinophilic material in the dermis, along with apple-green birefringence under polarized light, are diagnostic of PCA. The treatment options for PCA are vast, and none has proven ideal.

Conclusion

Primary cutaneous amyloidosis mainly presents in lichen, macular, or nodular variants, but other variants have also been reported. The diagnosis involves both clinical and histological analyses. Treatment aims at relieving itching or removing amyloid deposition, but no effective treatment is currently available.
References


Case Report: Renal Cell Carcinoma Presenting as Cutaneous Metastasis to the Scalp

Jessica Newburger, DO,* Charles Perniciaro, MD,** Karthik Krishnamurthy, DO***

* Dermatology Resident, 2nd Year, Park Avenue Dermatology/Orange Park Medical Center, Orange Park, FL
** Dermatopathologist, Aurora Diagnostics/Bernhardt Laboratories, Jacksonville, FL
*** Program Director, Dermatology Residency, Park Avenue Dermatology/Orange Park Medical Center, Orange Park, FL

Disclosures: None
Correspondence: Jessica Newburger, DO; Jessica.newburger@gmail.com

Abstract

Although renal cell carcinoma (RCC) is among the top ten most common malignancies in both men and women, cutaneous metastasis is very unusual. We report a man who presented to the dermatology clinic with a metastatic lesion of RCC on the scalp, which was the initial presentation of his disease.

Introduction

In both men and women, renal cell carcinoma (RCC) is among the ten most common malignancies.1 In the United States, 62,700 new cases of RCC were predicted for 2016, with 14,240 deaths.2 RCC has a male predominance, and the peak incidence occurs in the sixth and seventh decades.1 The classic presentation of RCC includes the triad of flank pain, hematuria, and a palpable abdominal mass,3 though the triad is only seen in approximately 10% of patients.4 Approximately 30% of patients with RCC develop metastasis, and the most common metastatic sites are the lungs, liver, bone, brain and lymph nodes.5 Cutaneous metastasis in RCC is rare, having an estimated incidence of 3.4%, and it usually presents as a late metastatic manifestation, not as the initial presentation.6 Approximately 30 cases of scalp metastasis of RCC have been reported in the literature.7 We report a man with RCC metastasis to the scalp as the initial presentation of his disease.

Case Report

A 54-year-old Caucasian male presented with a lesion on his scalp that had developed and enlarged over seven months. On examination, the patient had a solitary, 3.0 cm, friable, erythematous to violaceous nodule of the right parietal scalp (Figure 1). Our initial differential diagnosis included Merkel cell carcinoma, angiosarcoma, atypical fibroxanthoma, and pyogenic granuloma. An excisional biopsy was performed. Characteristic clear cell features of RCC were seen on the hematoxylin and eosin (H&E) sections, and a diagnosis of metastatic RCC was suggested, then subsequently confirmed by immunohistochemistry. These metastatic clear cells of RCC demonstrated an abundance of fragile, finely vacuolated, translucent cytoplasm, a “lacy” appearance due to irregularly sized vacuoles, and indistinct cell borders (Figure 2a). Tumor cells stained positive with pan-cytokeratin (AE1/AE3), vimentin, and RCC antibody (Figures 3, 4). The cells failed to stain with Mart-1, S100 protein, Sox 10, cytokeratin 7, and cytokeratin 20.

Following the results of the skin biopsy specimen, a CT scan of the abdomen was performed and revealed an 8.4 cm x 6.8 cm x 7.2 cm mass in the lower pole of the left kidney (Figure 5). A left nephrectomy was accomplished, and the mass was determined to be a primary clear cell RCC of histologic grade G3-G4. The microscopic features of the primary tumor were similar to those seen in the skin metastasis (Figures 2a, 2b). Cells of RCC generally tend to have a low nuclear-to-cytoplasmic ratio as well as round nuclei with anisokaryosis.8 The tumor extended into the perineal fat, and the patient was staged as pT3aN0.

Figure 1. Metastatic renal cell carcinoma of the scalp. Note vascular appearance.

Figure 2a. H&E 100x: a) High-power photomicrograph of metastatic RCC on the scalp showing abundant clear cells and vascular stroma; b) comparison photomicrograph of primary RCC from nephrectomy.

Figure 2b

Figure 3. H&E 20x: Tumor cells prominently stained with Vimentin.

Figure 4. H&E 40x: RCC immunohistochemistry positive in tumor cells.

Figure 5. CT scan demonstrating primary renal cell carcinoma of the left kidney (red arrow).
CASE REPORT: RENAL CELL CARCINOMA PRESENTING AS CUTANEOUS METASTASIS TO THE SCALP

Buffalo Grove, IL: Arch Pathol Lab. 2018

Objective: Metastatic renal cell carcinoma (RCC) is relatively rare, constituting less than 10% of metastatic disease. This case describes a unique presentation of RCC metastatic to the scalp which prompted a thorough investigation of the primary lesion.

Discussion: Metastatic RCC lesions are well-circumscribed, cutaneous nodules that can reflect the primary lesions’ histologic appearance. Although metastatic spread is common, the head and neck region is more commonly affected in RCC, while the scalp is very rarely involved. The incidence of metastatic RCC presenting to the head and neck region appears to vary between 0% to 8% of cases, with the scalp less commonly affected. Unusual locations of metastasis may delay diagnosis of the primary lesion.

Conclusion: A case of metastatic RCC of the scalp is described. The diagnosis was confirmed immunohistochemically with the aid of multiplex analysis. The potential utility of PD-L1 immunostains in the diagnosis of metastatic RCC is also discussed.

References:
News Release

For Immediate Release: June 7, 2017

Mark J. Holzberg, M.D.

Receives Dermatology Foundation Practitioner of the Year Award

At its annual meeting of membership in Orlando, FL, the Dermatology Foundation presented Mark J. Holzberg, M.D. with the prestigious 2016 Practitioner of the Year Award. The award recognizes Dr. Holzberg’s exemplary service as a private practitioner and his significant contributions to the specialty through leadership and teaching.

“Mark is the quintessential practitioner of dermatology,” says a colleague who has known Dr. Holzberg since medical school. “Simply put— he is outstanding.” This well-rounded Atlanta-based private practitioner, volunteer teacher, nail expert, and impassioned advocate for the specialty is highly regarded. Another colleague calls Dr. Holzberg “one of the finest, most intelligent dermatologists in the private practice of our specialty.” Yet another calls him “a key member of Emory’s outstanding volunteer clinical faculty and one of our most valued teachers, and the consummate community physician who gives constantly of his talent and enthusiasm for dermatology on a daily basis.”

Dr. Holzberg chose to stay in Atlanta after completing medical school and then his residency at Emory University School of Medicine 30 years ago. His clinical practice in the Atlanta metropolitan area remains the focus of his vibrant and multifaceted career because of the value he places on the relationships he builds with his patients. He is a volunteer teacher of medical students and residents at Emory, and an internationally recognized expert in nail disease who runs the Nail Clinic that he founded 30 years ago at Grady Hospital—a public hospital in the Emory system where he is also an attending dermatologist. Dr. Holzberg teaches at dermatology meetings and has co-authored a seminal textbook and chapters on nail diseases. He finds time to contribute to the dermatology community (including the presidency of local and regional
INDICATIONS AND USAGE: ULTRAVATE® (halobetasol propionate) Lotion, 0.05% is indicated for the topical treatment of plaque psoriasis in patients 18 years of age and older. Treatment beyond 2 weeks is not recommended, and the total dosage should not exceed 50 grams per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Discontinue therapy when control is achieved. If no improvement is seen within 2 weeks, reassessment of the diagnosis may be necessary.

IMPORTANT SAFETY INFORMATION
PRECAUTIONS: In a study of 20 adult subjects with moderate to severe plaque psoriasis, ULTRAVATE® Lotion produced HPA axis suppression when used twice daily for 2 weeks in 5 out of 20 (25%) patients. If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal, rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue ULTRAVATE® Lotion if allergic contact dermatitis is established. If concomitant skin infections are present or develop, an appropriate antimicrobial agent should be used. If a favorable response does not occur promptly, the use of ULTRAVATE® Lotion should be discontinued until the infection has been adequately treated. The treated skin area should not be bandaged, covered, or wrapped with occlusive dressings, unless directed by the physician. The safety and effectiveness of ULTRAVATE® Lotion in patients younger than 18 years of age have not been established. ULTRAVATE® Lotion is for external use only. Avoid use on the face, scalp, groin, or axillae.

ADVERSE REACTIONS: In controlled clinical trials, the most frequent adverse events reported for ULTRAVATE® Lotion included telangiectasia, application site atrophy, and headache in 1% of patients. Less frequently reported adverse reactions were application site discoloration, herpes zoster, influenza, nasopharyngitis, otitis media acute, throat infection, wound, and increased blood pressure. This preparation is not for ophthalmic, oral, or intravaginal use. For external use only.

Please see Brief Summary of full Prescribing Information on following page.

If you experience any Adverse Events you are encouraged to report them to the Drug Safety Department at 1-800-406-7984 or email Drug.Safety@ranbaxy.com. You can also report to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
ULTRAVATE (halobetasol propionate) Lotion

BRIEF SUMMARY:
See package insert for full prescribing information.

1. INDICATIONS AND USAGE
ULTRAVATE lotion is indicated for the topical treatment of plaque psoriasis in patients eighteen (18) years of age and older.

2. DOSAGE AND ADMINISTRATION
Apply a thin layer of ULTRAVATE lotion to the affected skin twice daily for up to two weeks. Rub in gently. Discontinue therapy when control is achieved. If no improvement is seen within two weeks, reassessment of diagnosis may be necessary.

3. CONTRAINDICATIONS
Do not use with occlusive dressings unless directed by a physician.

4. CONTRAINDICATIONS
None.

5. WARNINGS AND PRECAUTIONS
5.1 Effects on Endocrine System
ULTRAVATE lotion is a topical corticosteroid that has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis.

Systemic effects of topical corticosteroids may include reversible HPA axis suppression, with the potential for glucocorticoid insufficiency. This may occur during or upon withdrawal of treatment of the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) suppression with ULTRAVATE lotion was evaluated in 120 adult subjects with moderate to severe plaque psoriasis involving >20% of their body surface area. ULTRAVATE lotion produced HPA axis suppression when used twice daily for two weeks in 5 out of 20 (25%) adult patients with plaque psoriasis. Recovery of HPA axis function was generally prompt with the discontinuation of treatment [see Clinical Pharmacology (12.2)].

Because of the potential for systemic absorption, use of topical corticosteroids, including ULTRAVATE lotion, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, prolonged use, occlusive use, use on an already skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An ACTH stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids.

Systemic effects of topical corticosteroids may also include Cushing's syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to corticosteroids.

Pediatric patients may be more susceptible than adults to systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see Use in Specific Populations (8.4)].

5.2 Local Adverse Reactions
Local adverse reactions from topical corticosteroids may include atrophy, strie, telangiectasias, burning, itching, irritation, dryness, folliculitis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, secondary infection, and miliaria. These may be more likely to occur with occlusive use, use on more than 20% of the body surface area, and use of higher potency corticosteroids, including halobetasol propionate.

Some local adverse reactions may be irreversible.

5.3 Concomitant Skin Infections
Use of an appropriate antifungal agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of ULTRAVATE lotion until the infection has been adequately treated.

5.4 Allergic Contact Dermatitis
Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal adequately treated.

6. ADVERSE REACTIONS
6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

During randomized, controlled, blinded clinical trials 277 adults with plaque psoriasis were treated with ULTRAVATE lotion twice daily for up to two weeks (up to approximately 50 grams/week). Treatment beyond two weeks is not recommended and the total dosage should not exceed 50 grams (50 mL) per week because of the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis [see Warnings and Precautions (5.1)].

Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with ULTRAVATE lotion twice daily for up to two weeks and more frequently than in vehicle-treated subjects.

Table 1. Adverse Reactions Occurring in >1% of Subjects Treated with ULTRAVATE Lotion for up to Two Weeks

<table>
<thead>
<tr>
<th>Reaction</th>
<th>ULTRAVATE Lotion (N=277)</th>
<th>Vehicle Lotion (N=259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Application site atrophy</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Headache</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Less common adverse reactions (incidence less than 1% but greater than 0.1%) that occurred in subjects treated with ULTRAVATE lotion included application site discoloration, herpes zoster, influenza, nasopharyngitis, otitis media acute, throat infection, wound, and increased blood pressure.

Table 2 presents adverse reactions that occurred in at least 1% of subjects treated with halobetasol propionate lotion at dose concentrations from 0.05% to 0.1% or from 0.25 to 0.5 mg/kg/day of halobetasol propionate resulted in a toxicity profile consistent with long-term exposure to corticosteroids including adrenal atrophy, histopathological changes in several organ systems indicative of severe immune suppression, and opportunistic fungal and bacterial infections. A no observable adverse effect level (NOAEL) could not be determined in this study. Although clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis. Halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the Chinese hamster CHO/HGPRT assay, in the mouse micronucleus test, in the sister chromatid exchange test in somatic cells of the Chinese hamster, or in the chromosomal aberration test in somatic cells of Chinese hamsters. Positive mutagenicity effects were observed in two genotoxicity assays: Chinese hamster nuclear anomaly test and mouse lymphoma gene mutation assay in vitro.

Studies in the rat following oral administration at doses levels up to 50 µg/kg/day indicated no impairment of fertility or general reproductive performance.

17. PATIENT COUNSELING INFORMATION
This information is intended to aid in the safe and effective use of this medication. It is not a disclosure of all administration instructions or all possible adverse or unintended effects.

Advis patients using ULTRAVATE lotion of the following information and instructions:

Important Administration Instructions
Instruct patients to discontinue ULTRAVATE lotion when psoriasis is controlled. ULTRAVATE lotion should not be used for longer than 2 weeks. Advise patients to contact the physician if no improvement is seen within 2 weeks. Inform patients that total dosage should not exceed 50 grams per week [see Dosage and Administration (2)].

Instruct patients to avoid bandaging, wrapping, or otherwise occluding the treatment areas, unless directed by physician. Advise patients to avoid use on the face, scalp, groin, or axillae [see Dosage and Administration (2)].

Breastfeeding women should not apply ULTRAVATE lotion directly to the nipple and areola to avoid direct infant exposure.

8. USE IN SPECIFIC POPULATIONS
8.1 Pregnancy Risk Summary
There are no data on topical halobetasol propionate use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. In animal reproduction studies, halobetasol propionate administered systemically during organogenesis to pregnant rats at 13 and 33 times the human topical dose and to pregnant rabbits at 3 times the human topical dose resulted in teratogenic and embryotoxic effects [see Data]. The clinical relevance of the animal findings is not clear.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation
Risks Summary
There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after topical application to women who are breastfeeding.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ULTRAVATE lotion and any potential adverse effects on the breastfed infant from ULTRAVATE lotion or from the underlying maternal condition.

Clinical Considerations
Advise breastfeeding women not to apply ULTRAVATE lotion directly to the nipple and areola to avoid direct infant exposure.

8.4 Pediatric Use
Safety and effectiveness of ULTRAVATE lotion in patients younger than 18 years of age have not been established.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing’s syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see Warnings and Precautions (5.1)].

HPA axis suppression, Cushing's syndrome, linear growth retardation, delayed weight gain, and intrauterine growth retardation have been reported in children receiving topical corticosteroids.

Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papillae [see Warnings and Precautions (5.7)].

8.5 Geriatric Use
Clinical studies with ULTRAVATE lotion included 89 subjects aged 65 years and over. No overall differences in safety or effectiveness were observed between these patients and those younger than 65 years. Clinical studies of ULTRAVATE lotion did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

10. OVERDOSAGE
Topically applied ULTRAVATE lotion can be absorbed in sufficient amounts to produce systemic effects [see Warnings and Precautions (5.1)].

13. NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate. In a 90-day repeat-dose toxicity study in rats, topical administration of halobetasol propionate lotion at dose concentrations from 0.05% to 0.1% or from 0.25 to 0.5 mg/kg/day of halobetasol propionate resulted in a toxicity profile consistent with long-term exposure to corticosteroids including adrenal atrophy, histopathological changes in several organ systems indicative of severe immune suppression, and opportunistic fungal and bacterial infections. A no observable adverse effect level (NOAEL) could not be determined in this study. Although clinical relevance of the findings in animals to humans is not clear, sustained glucocorticoid-related immune suppression may increase the risk of infection and possibly the risk of carcinogenesis. Halobetasol propionate was not found to be genotoxic in the Ames/Salmonella assay, in the Chinese hamster CHO/HGPRT assay, in the mouse micronucleus test, in the sister chromatid exchange test in somatic cells of the Chinese hamster, or in the chromosomal aberration test in somatic cells of Chinese hamsters. Positive mutagenicity effects were observed in two genotoxicity assays: Chinese hamster nuclear anomaly test and mouse lymphoma gene mutation assay in vitro.

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Ranbaxy Laboratories Inc.
Jacksonville, Florida 32257
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