The Scar
Osteopathic Principles Incarnate

Also in this issue:
Proteus Syndrome in a 14-year-old Male
Painful, Pruritic Blisters Exacerbated by Heat and Sweating
Marijuana: An Unusual Cause of Fixed Drug Eruption
# Table of Contents

<table>
<thead>
<tr>
<th>Volume 32</th>
</tr>
</thead>
</table>

**JAOC Editors** ........................................................................................................................................................................4

**Letter from the President** .......................................................................................................................................................5

**Letter from the Executive Director** ..........................................................................................................................................6

**Letter from the Editor-in-Chief** ..................................................................................................................................................7

**FEATURE ARTICLE:**
The scar as a representation of the osteopathic principles ...........................................................................................................11

*Sarah Belden, DO, Jenifer Lloyd, DO, Michael Rowane, DO*

**EDITOR’S PICKS:**
Marijuana: An Unusual Cause of Fixed Drug Eruption ..................................................................................................................16

*Christina Steinmetz-Rodriguez, DO, Brent Schilling, MD*

Painful, Pruritic Blisters Exacerbated by Heat and Sweating .........................................................................................................19

*Collin M. Blattner, BS, Dustin V. Wilkes, DO, Dongkun Chang, MD*

Proteus Syndrome: Case Report and Review ..................................................................................................................................21

*Holly Kanavy, DO, Cindy Hoffman, DO*

**ORIGINAL ARTICLES AND CASE REPORTS:**
Reactive Keratoacanthoma Responding to Excision and Healing by Secondary Intention .....................................................................24

*G. Trey Haunson, DO, Mariana A. Phillips, MD, FAAD, FACMS, Douglas J. Grider, MD, FCAP, Daniel S. Hurd, DO, FAOCD*

A Case of Cutaneous Rosai-Dorfman Disease ....................................................................................................................................27

*Donna Tran, DO, Gabriel Guerrero, DO, Paul Shitabata, MD, Navid Nami, DO*

Pathogenesis of Pruritic Disorders and Mechanisms of Phototherapy ................................................................................................29

*Soham Chaudhari, BA, Argentina Leon, MD, Ethan Levin, MD, Om Chaudhari, John Koo, MD*

The Cutaneous Manifestations of Metastatic Lung Cancer: Case Report and Review ...........................................................................34

*Sarah Ferrer-Bruker, DO*

Loose Anagen Syndrome in a 2-year-old Female: A Case Report and Review of the Literature ................................................................37

*Mathew Koehler, DO, Anne Nguyen, MS, Navid Nami, DO*

Anetoderma Secondary to Mid-dermal Elastolysis ..............................................................................................................................40

*Gabriela A. Maloney, BS, Jane James, MD, PhD, Michael Welsch, MD, Marylee Braniecki, MD*

Generalized Linear Porokeratosis: A Case Report and Discussion .......................................................................................................42

*Stephanie Blackburn, DO, Zaina Rasbid, DO, John Moad, MD, Michelle Duff, DO, Jason Barr, DO*

Permanent Imiquimod-induced Depigmentation ...................................................................................................................................45

*Anne Donato, MD, J. Kate Jackson, PA-C, Laura Sandoval, DO, Jonathan S. Crane, DO, FAOCD*

Telangiectasia Macularis Eruptiva Perstans: A Case Presentation and Discussion ..................................................................................47

*Sergey Petrosian, BS, Shane Mochan, MD, Anna Slobodskaya, DO, Peter Saietta, DO*

Hypomelanosis of Ito in Two Infants: A Case Series with Literature Review ......................................................................................49

*Mathew Koehler, DO, Nicole Rouse, BS, Tarin Molly Koehler, DO, Navid Nami, DO*

Phacomatosis Cesioflammea: A Case Report of a Newborn with an Unusual Mongolian Spot and Port Wine Stain ..............................................................................52

*Joy Ishii Zarandy, DO, Sara Clark, MD, Katherine Shew, MD*

**PERSPECTIVES:**
While Serving Abroad, Remembering the “Why” Behind Dermatology .............................................................................................56

*Leela Athalye, DO*

Letter to the Editor: Wegener’s Granulomatosis Eponym ..................................................................................................................58

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DJACD EDITORS
Dear Members of the AOCD,

Welcome to another issue of our journal! Under the leadership of Dr. Karthik Krishnamurthy and his dedicated board of editors, we are seeing another issue of the Journal of the American Osteopathic College of Dermatology come to fruition.

Speaking of issues coming together, this past February, I was invited to represent the AOCD at a meeting hosted by AAD President Dr. Brett Coldiron. The topic of discussion was the proposition to create Board certification for “micrographic surgery and dermatologic oncology.” This proposal was favored by many of the organizations represented there. The discussion focused on the potential outcome of mending the division between “fellowship trained” and “society trained” Mohs surgeons with a new category of “Board certified” Mohs surgeons. It was noted that the new Board certification would bring recognized expertise in cutaneous “surgery” and “oncology” to the house of dermatology. This recognition by other medical specialties within the ABMS would further elevate the status of dermatology within the broader house of medicine.

However, this effort to define surgical subspecialization is not without its drawbacks. The further division of dermatology into “medical” and “surgical” dermatology is a potential outcome. This point was emphasized by some of the attendees. Concerns about the increased potential legal risks when a general dermatologist decides to perform an excision or electrodesiccation and curettage also were raised. In the case of a bad outcome, the decision is more difficult for a general dermatologist to defend legally if a micrographic surgeon/dermatologic oncologist was available.

It was proposed that there be a five-year grandfather period during which any provider who practices Mohs surgery at least 20 percent of the time may take the examination. The candidate also will need to be board-certified by the American Board of Dermatology. However, ABD certification will not apply to our members who are board-certified by the AOBD. We will continue to monitor this effort to create a subspecialty board certification and how it will impact osteopathic dermatologists and the field of dermatology as a whole.

In the meantime, I look forward to seeing many of you at our spring meeting in Charlotte, North Carolina. Dr. Dan Ladd, the program chair, has put together a highly educational program. The latest dermatological concepts and practice-management pearls will be presented. In addition, we are privileged to have Dr. Nicole Owens, chair of ACGME’s Residency Review Committee for Dermatology, address our membership.

On a final note, I would like to say that the future of our College, as with any College, is dependent on its members. To face the challenges ahead, I encourage you to reach out to the AOCD Board of Trustees to share your thoughts and volunteer your time. We are looking for members who would like to play significant roles in the leadership of the AOCD. In the years to come, the survival of our College will impact our future recertification process. With the ACGME merger, our future is in a state of flux. Only through the dedication of our members will we be able to chart our future, rather than have it decided for us.

Rick Lin, DO, MPH, FAOCD
President, American Osteopathic College of Dermatology
Hello, Everyone,

It seems as though winter has lasted forever, but spring is finally here!

We’ve had a busy start to the year. Drs. Suzanne Sirota Rozenberg, Lloyd Cleaver, Rick Lin and I attended the AOA Osteopathic Medical Education Leadership Conference in January. In February, Dr. Lloyd Cleaver and I attended the ACGME’s Annual Educational Conference. Both of these meetings provided valuable updates on the Single Accreditation System, or SAS. The information regarding SAS can be found on the AOA and ACGME websites. We encourage everyone to log on and familiarize themselves with the single accreditation system:

http://www.osteopathic.org/inside-aoa/single-gme-accreditation-system/Pages/default.aspx
http://www.acgme-i.org/Requirements-and-Process-Overview/What-is-Accreditation

Programs may begin to apply for pre-accreditation status in April 2015.

In February, the ACGME announced that Dr. Stephen Purcell was appointed to the Dermatology Residency Review Committee. We’re excited to have Dr. Purcell represent the AOCD and the osteopathic profession. Dr. Purcell’s leadership in the AOCD has been invaluable, and he is a true advocate for osteopathic dermatologists.

During the General Membership Meeting recently held in Seattle, the membership voted to accept the changes to the bylaws that had been presented last summer. On March 2, we received word that the AOA approved our proposed changes. These changes are now in effect and can be found on our website at: https://aocd.site-ym.com/?page=ByLaws.

March and April have been busy with the AAD meeting and our Spring Conference in Charlotte, NC. A panel discussion on “Unified U.S. Dermatology Training Accreditation and the Unification of the Specialty of Dermatology” took place at the AAD Annual Meeting on Sunday, March 22. Be sure to look for highlights of these meetings in upcoming Dermline publications.

Exciting changes are in store for our Fall Conference. Our meeting is scheduled for October 16th through 19th, 2015, in Orlando at the Loews Royal Pacific Resort. An information packet with further details will be mailed to our members about the changes happening with this meeting.

Please call or email the AOCD office (660-665-2184, dermatology@aocd.org) if you have questions or need assistance.

Sincerely,

Marsha Wise
Executive Director, American Osteopathic College of Dermatology
Dear Readers,

Many of you are familiar with the “Blurred Lines” controversy in which the Marvin Gaye estate won judgment for copyright infringement. Many artists are outraged, fearing this will set a dangerous precedent, claiming that all music is derivative in some way. What is considered “original” versus “copied” can be ill-defined -- which side does “was-influenced-by” sit on? This has made me ponder how we authors face this same issue every time we prepare a manuscript. We all gasp at the word “plagiarism,” look over our shoulders as we whisper the word, almost as if we would with “murder.”

And yet almost everyone reading this column has infringed on someone else’s work, almost certainly without realizing it. It’s not something we would ever consciously do.

It is exceptionally difficult to find ways to incorporate relevant information in an original way when citing a resource, especially since there is a limited and acceptable way in which we are trained to communicate certain data in the medical field. The online resource iThenticate is a service we can use to check for verbatim overlap when preparing our manuscripts, but this only gets us so far.

According to our Assistant Editor:

Copying another author’s words verbatim is only the most obvious type of plagiarism. Let’s say you change a couple of words in a sentence -- that’s still plagiarism, even if you attribute it to the source. The new sentence is too close to the original. In addition to attribution, it needs quotation marks around all of the words not changed. (If you ask me, it’s easier to just use the original and put quotes around the whole thing.) If you significantly change both sentence structure and words, a.k.a. paraphrase, it’s also plagiarism -- unless you attribute it. Paraphrasing is fine as long as you give credit to the source. Plagiarism isn’t only about another author’s words, though. You can plagiarize yourself. And regardless of the words you use, restating another author’s idea or interpretation without attribution is plagiarism (and a much more complicated subject).

I guess imitation is not always the highest form of flattery.

If you’d like to explore this more, try “Avoiding plagiarism, self-plagiarism, and other questionable writing practices,” by Miguel Roig, PhD (https://ori.hhs.gov/avoiding-plagiarism-self-plagiarism-and-other-questionable-writing-practices-guide-ethical-writing). It speaks specifically to science writing.

Fraternally,

Karthik Krishnamurthy, DO, FAOCD
Editor-in-Chief, Journal of the American Osteopathic College of Dermatology
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The Scar as a Representation of the Osteopathic Principles

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Abstract

A scar is the manifestation of the skin’s healing process following an injury. It can be a cosmetic concern to some individuals while dismissed and disregarded by others. New treatment options continue to be investigated, but no solution currently exists for erasing a problematic scar. By viewing the scar as a source of somatic dysfunction using the four osteopathic principles, the dermatologist is able to employ the use of osteopathic manipulative treatment techniques as an adjunctive tool in scar management. Here we explore the scar through an osteopathic lens and describe treatment strategies that have been shown to be effective in improving the somatic dysfunction caused by the presence of a scar.

Introduction

A scar, or cicatrix, is the end result of the wound repair mechanism in adults and children following an injury, either traumatic or surgical, beyond the epidermis. It is the consequence of a surgical incision and is inevitable despite the surgeon’s best efforts to hide it within the skin’s natural contour lines.

It is a common lesion encountered in dermatology, and it is the source of much cosmetic concern. More than 230 million surgical procedures are performed around the world each year, all of which result in cutaneous wounds that heal with scars. A recent survey indicated that 91% of patients who underwent a routine surgical procedure would value any improvement in scarring. Scars also affect other body systems including the musculoskeletal system or deep viscera in the form of adhesions. They are also linked to pain and depression.

The cosmetic outcome of a scar and its subsequent implications on a patient’s overall wellbeing is of primary importance in dermatology. Patients are often left desperate for treatment options after first-line treatments—such as silicone sheeting, pressure dressings and intradermal steroids—fail. Osteopathic manipulative treatment (OMT) is a non-invasive, cost-effective therapy designed to restore the natural homeostasis of the tissue. This repair mechanism is divided into a series of stages, each having unique characteristics.

The first stage of wound healing is known as the inflammatory phase, where cytokines and inflammatory cells are recruited and infiltrate the site to destroy potential pathogens, remove debris, and initiate coagulation through the formation of an initial thrombus. The inflammatory pathway of wound healing, a large determinant of the outcome of a scar, has long been the focus of attack for anti-scarring research, but strategies that block inflammation alone have so far proved suboptimal with significant side effects.

The second stage, called proliferation, is characterized by the fibroblast cell. Fibroblasts are responsible for producing collagen, which provides the structure to the wound and creates a new matrix—the groundwork of a scar. Remodeling, the final stage of wound repair, begins at about two to three weeks following trauma and can last for years depending on the size of the wound. During this stage, fibroblasts are responsible for organizing and cross-linking the collagen, increasing the strength of the new site, and causing contraction of the wound edges in the process.

The appearance of a scar is influenced by many factors: the depth of trauma (injury limited to the epidermis can heal without scarring), the location (the chest is an area more susceptible to scar formation), whether the patient is at risk of keloid or hypertrophic scarring (genetics, ethnicity, etc.), age, and nutritional and vitamin deficiencies.

It is important to appreciate that the dynamics between the wound repair process and the scar do not end immediately. Rather, an interplay between the traumatized tissue, the scar, and the surrounding non-traumatized tissue results in altered tissue arrangement that manifests as tissue texture changes contributing to the scar’s appearance.

Discussion

Osteopathy and scars

Principle 1. The body is a unit; the person is a unit of body, mind, and spirit.

This osteopathic principle represents how a scar can affect a person’s entire wellbeing. Much like the saying “a scar is more than skin deep,” a scar may have a deeper value to one person but not to another. It can serve as a permanent reminder of the past, whether it is pleasant or unpleasant, that extends to the body, mind and spirit.

It is known that the connection between the skin and the mind is a powerful one. For example, stress can exacerbate psoriasis and cause acne breakouts. Stress can also play a role in scar formation. Furtado et al. found that psychological stress influences the rate of recurrence of keloids when stress is experienced the day before keloid excision, increasing the chances of keloid recurrence by 34%. The location of the scar and the patient’s age or gender are factors that influence its impact. A scar on the chest of a young female, for example, may cause increased self-consciousness and impact the clothing she chooses to wear.

There is a variety of psychosocial comorbidities associated with scarring. Depression is the predominant finding in patients suffering from burn scars. A combination of anxiety, depression and PTSD-related disorders were seen in 64% of the patients who developed scars following ICU admission for severe soft-tissue infections in one study. Other psychosocial characteristics of patients with scars, particularly within the burn population, include avoidance of social interaction, loneliness and living a solitary lifestyle.

Thus, the first step in scar management is to consider the whole patient. The stressors and history behind the scar are important to address prior to subsequent treatment. Approaches such as suggesting stress-management techniques peripherally may help improve the chances of a better scar outcome. Counseling or referring to psychiatry is important for patients displaying psychological symptoms. Education plays a helpful role, such as teaching the patient the importance of keeping the scar covered from the sun and applying sunscreen after the surgery. It is important to consider the whole patient when performing a procedure; the patient’s age, incision length and location should be respected in order to ensure the best possible scar outcome.
This mechanism can best be explained through the osteopathic bioelectric model of fascia as described by Judith O’Connell, DO, FAAO, which illustrates the important relationship between the dermis and its underlying fascia.\textsuperscript{15,16} Fascia is found between the deep and superficial adipose layers and is connected to the dermis through perpendicular septa of fibrous extensions.\textsuperscript{17} It communicates with the dermis via bioelectric currents through the extracellular fluid, which is considered a homeostatic relationship within the skin.\textsuperscript{18,19}

The presence of a scar applies extra mechanical tension to the tissue, causing a disruption of the normal homeostatic signaling between the fascia and dermis. The collagen within the scar itself also releases microelectrical-potential changes into the extracellular fluid.\textsuperscript{15,18} This aberrant bioelectric current not only alters the local architecture of the dermis and fascia but also the arrangement of surrounding tissue (neural, muscular, vascular, and lymphatic), resulting in changes such as stiffness, altered motion, pain, and edema that can be restored using OMT.\textsuperscript{3,15,16,19}

Thus, it is important to acknowledge that the wound repair process and its end product, the scar, is not a static process. Rather, there are many dynamic homeostatic elements that are ongoing following scar formation that contribute to the overall somatic dysfunction and scar appearance.

**Principle 3. Structure and function are reciprocally interrelated.**

This principle stems from Dr. Still’s belief that abnormal tissue structure is likely to result in disruptions in tissue function and vice versa. A scar disrupts the normal architecture and function of surrounding skin. The clinical result is an area of somatic dysfunction. By its standard definition, chronic somatic dysfunction of a scar* is a condition affecting normal facial expression.\textsuperscript{18}

Muscular dysfunction may be observed in the dermatological arena following the formation of facial scars. The SMAS is a structure that ensheds the facial muscles and neurovasculature and plays an intricate role in coordinating and exaggerating facial expressions.\textsuperscript{22} If a scar extends to the level of the SMAS, the thickened fibrosis may cause stiffness of the fascia, which may lead to altered range of motion of the facial muscles, affecting normal facial expression.\textsuperscript{18}

**Principle 4. Rational treatment is based on an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function.**

Treatment relies on a full understanding of how a scar can affect the entire body while acknowledging the first-line evidence-based treatment strategies and knowing alternatives for more refractory cases. First-line treatment for scars includes a variety of options such as silicone sheeting, pressure dressings, intralesional steroids, 5-FU, bleomycin, and verapamil, as well as laser therapy, localized radiotherapy, micro-needling, and intralesional cryotherapy for the more refractory cases.\textsuperscript{23} Osteopathic manipulative therapy is a cost-effective and non-invasive treatment option that may be employed as an adjunct and for those scars resistant to the standard therapy. Several techniques may be utilized and have been shown to be effective in improving the appearance of a scar and its surrounding tissue.

It is important for the osteopathic dermatologist to gain an understanding of which scar characteristics are clinically relevant for OMT and the rationales for treatment based on the models of osteopathic care.

**Identifying a scar to be treated**

The first step in effective OMT is to properly identify whether a scar and its surrounding tissue would benefit from treatment. Its level of acuity must be assessed. It is important to not manipulate acute scars, i.e., hot, boggy, tender or erythematous scars, or those exhibiting venous congestion/edema. Manipulation of an acute scar would delay the wound healing process, which would worsen the structure and function dynamics of the scar.\textsuperscript{24}

The scar should exhibit chronic somatic dysfunction. By its standard definition, chronic somatic dysfunction is “impairment or altered function of related components of the somatic (body framework) system characterized by tenderness, itching, fibrosis, and tissue contraction; identified by TART”.\textsuperscript{25} The forces exerted by the scar to the surrounding tissue, as described above, may manifest as tissue texture changes listed in Table 1. The extent of the tissue texture changes and the restricted and resistance (pathological barriers) of the deeper tissue may be determined by palpation.\textsuperscript{24}

<table>
<thead>
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<th>Table 1. Tissue texture changes associated with chronic somatic dysfunction of a scar*</th>
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<td>Ropiness: cord-like, fibrotic feeling (in the scar itself)</td>
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<td>Stringiness: fine or string-like myofascial structures</td>
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<tr>
<td>Firmness, hardening</td>
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<tr>
<td>Temperature changes</td>
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<tr>
<td>Increased/decreased moisture</td>
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<td>Lymphedema</td>
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*Lymphedema is a common finding associated with the chronic somatic dysfunction of a scar. The term “scar lymphedema” is used to describe the localization of lymphatic fluid around the scar site due to the damage of the lymphatic channels and pathways caused by the surgical incision.\textsuperscript{25} The difference between edema and lymphedema surrounding a scar is based upon location of the swelling. With lymphedema, swelling affects only the “upstream” side of a healed incision (such as the circumscribed central area of a U-shaped scar), whereas nonspecific edema will surround the entire scar.\textsuperscript{26} “Active scar” is another term used to describe a scar that would benefit from OMT; it is “active” if it exhibits soft-tissue changes characterized by increased skin drag, owing to increased moisture (sweating), impaired skin stretch, and a thickened skin fold.\textsuperscript{24} The exact timeline of when it is appropriate to treat scars using OMT has not been formally established.\textsuperscript{22} The use of pressure therapy on scars after burn injury showed that earlier treatment (scar treated <6 months after burn injury) resulted in better outcome than those treated later.\textsuperscript{28} It has been proposed that noninvasive scar management, such as manipulation, typically occur within the early maturation phase of the wound healing process in order to improve scar outcome and accelerate time of scar maturity.\textsuperscript{29} More studies are needed to investigate the most appropriate time to implement OMT.

**Treatments**

The biomechanical model and the respiratory-circulary model of osteopathy help guide the dermatologist to select the most appropriate OMT therapies. Based on these models, soft-tissue techniques, myofascial release and a lymphatic approach to the scar are considered. The therapeutic principles of the models in
Biomechanical Model: Soft Tissue Techniques and Myofascial Release

The goal of the biomechanical model seeks to address problems with the soft tissue, muscle and fascia by removing the restrictive forces of the tissue. As previously mentioned, there are many restrictive forces or tissue texture abnormalities that may be palpated surrounding the scar. Soft tissue OMT and scar (myofascial) release are two techniques that address these forces and have been shown to improve scar outcome.

Both techniques utilize the concept of pressure restoring balance to the scar. Physical pressure at the site of a scar causes local hypoxia, which induces the regeneration of fibroblasts, suppresses collagen production, and activates collagenase, which overall expedites collagen dismantling. The fibroblasts, which play a role in contracting collagen lattices, are relaxed through the pressure of manipulation. This relaxation results in increased microcirculation to the site owing to the restoration of tissue texture abnormalities. It has been shown that manipulation encourages collagen fibrils of the dermis to realign. The immediate result of these changes can be palpated through the form of a release.

There is a variety of soft-tissue techniques that may be used for treating scars. The treatment goals include increasing tissue elasticity, enhancing circulation to local fascial structures, improving local tissue nutrition and oxygenation, improving local immune response, and providing a general state of relaxation. Scar soft-tissue manipulation is distinguished from scar massage therapy in that it makes use of the barrier-and-release phenomenon; scar massage does not. Soft-tissue techniques used for scars include effleurage, skin rolling, stretching, and petrissage.

Effleurage is a light stroking soft-tissue technique that is used on more superficial scar tissue. McKay performed a five-week treatment of soft-tissue techniques including effleurage to improve the appearance and function of cleft-lip scars. Based upon patient subjective results, she found soft-tissue manipulation to be an effective means for increased patient satisfaction and improvement of the appearance of the scar.

Skin rolling is another soft-tissue technique. It involves lifting the skin away from the deeper structures and "rolling" the skin fold along the body. Pohl examined the changes in the structure of collagen in scars following...
Soft-tissue stretching along the site of a scar has also been shown to be effective in scar management. Soft-tissue stretch engages the barrier palpated along the distal ends of the scar while slowly stretching and releasing the surrounding tissue in multiple planes. The treatment led to decreased pain and increased tissue mobility in the majority of cases. The scar ends were found to be the most active sections of the scar, and treatment was aimed predominately at these sites.

Pettrissage, which is a deeper kneading and squeezing pressure, is considered to be an excellent soft-tissue technique for scars. Morien et al. investigated a combination of effleurage, pettrissage, stretching and rolling in a group of post-burn patients, which showed improvement in range of motion at the scar site and overall patient satisfaction. Field et al. compared a group of post-burn patients who received a combination of skin rolling, stretching and stroking to a group who received no manipulation. It was found that those in the manipulation group experienced a relief of pruritus, pain, anxiety and improvement in mood associated with their scarring.

“Scar release” is an indirect form of a myofascial-release technique that may be used to reduce asymmetric tension and restore functional balance to the stresses transmitted through a scar. It is utilized to engage deeper tissue such as muscle and fascia. Successfully releasing the deep fascial restriction and correcting the restrictive forces in turn activates surrounding bioenergetic tissue. It has been reported to be an effective technique in improving post-mastectomy axillary cord anchoring secondary to scar formation, leading to improvement of axillary-scar appearance and surrounding lymphedema.

Respiratory-Circulatory Model:

Diaphragm Release and Lymphatic Pump

Based upon the respiratory-circulatory model, lymphatic techniques are designed to remove impediments to lymphatic circulation and promote and augment the flow of lymph. As previously noted, lymphedema can be a prominent feature of the chronic scar; it may even be measured using lymphoscintigraphy. Mobilizing the tissue surrounding the scar can help improve circulation and the exchange of lymphatic fluids and metabolites, which can ultimately encourage the normal distribution of fibroblast and collagen.

The proposed application of lymphatic treatments to scars involves first opening the myofascial pathways to increase microcirculation to the site (via the soft-tissue techniques and myofascial release), and then treating the diaphragms. By definition, diaphragms occur at important anatomical crossroads in the body where curves and cavities change and where passage points for major circulatory and lymphatic vessels occur. Maximizing the motion of diaphragms helps to improve circulatory and lymphatic flow, which would be beneficial in the setting of a scar exhibiting lymphedema in the setting of chronic somatic dysfunction. In dermatology, the relevant diaphragms are both peripheral and central, based on the location of the scar as listed in Table 2. Clinical studies are needed in order to explore the outcome of diaphragm release and other lymphatic treatments for scars.

Table 2. Diaphragms to treat based on scar location

<table>
<thead>
<tr>
<th>Scar Location</th>
<th>Suggested Diaphragm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp, face, neck</td>
<td>Tentorium</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>Thoracic inlet</td>
</tr>
<tr>
<td>Chest, upper back</td>
<td>Palmar fascia</td>
</tr>
<tr>
<td>Abdomen, lower back,</td>
<td>Respiratory diaphragm</td>
</tr>
<tr>
<td>buttocks, pelvis</td>
<td>Pelvic diaphragm</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>Plantar fascia</td>
</tr>
</tbody>
</table>


Based on the location of the scar and patient history, choose the most appropriate diaphragm to treat, as noted in Table 2.

1. Using compression, distraction or the full deep respiration cycle, induce motion and note the different patterns of interaction between the normal and dysfunctional tissue response.
2. The dysfunctional pattern, whether a barrier or point of ease, should become apparent at the diaphragm, making the primary dysfunction at the scar evident, and a release should begin.
3. If treating using respirations, motion in the tissue should begin as a release occurs, with a new end point of motion manifesting.

Conclusion

By viewing the scar through an osteopathic lens, the dermatologist is able to gain an understanding of how the scar is more than just a fibrosis on the skin; it represents how one dermatological lesion can affect the entire person. It is an active participant within the homeostatic environment of the skin that can affect both structure and function of the human body. Based on available clinical data, osteopathic manipulative treatment should be considered in the dermatological arena as a therapeutic strategy for scar management. Further clinical studies are needed to establish the most effective OMT modalities and the most appropriate time to initiate and continue therapy.

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Introduction
First described by Burns in 1889, subsequently named "eruption erythemato-pigmentee fixe" by Brocq, the "fixed drug eruption" is one of the most common types of drug eruptions, and its incidence continues to increase over the years relative to other drug eruptions. The most characteristic findings of FDE are "lesions that recur at the same anatomic sites upon repeated exposure to an offending agent," according to Pai et al. A large number of drugs, including barbiturates, penicillin, sulfonamides, tetracycline, bismuth and iodides, have been linked to FDE. Marijuana use, however, remains an underreported cause of FDE. As legalization of marijuana in the United States becomes more widespread, it is important for clinicians to recognize the cutaneous manifestations of marijuana use. Because drug abuse carries a negative stigma, patients are not always immediately forthright in reporting their history of illicit drug use. By both recognizing cutaneous signs and routinely inquiring about illicit drug use, dermatologists can be the first to recognize signs of illicit drug use in patients, resulting in earlier treatment.

Case Presentation
A 32-year-old man presented to the dermatology clinic with complaints of recurring hyperpigmented patches on his face over the past year that were transient. He denied any pain, pruritis or discomfort. He noticed that the lesions would erupt in the same location on his face each time, on a monthly basis, and resolve in six to seven days. He denied any prior medical history and reported no medication use including over-the-counter medications.

Physical examination revealed a well-defined, 2 cm, circular hyperpigmented patch over his right zygoma with mild scaling at the periphery (Figure 1). Additionally, two 0.5 cm hyperpigmented macules bilaterally on the lower lip, and a 1 cm macule in the philtral ridge, were seen on examination (Figure 2).

Shave biopsy of the zygomatic lesion revealed interface vacuolar changes with dermal melanophages and some eosinophils, as well as near-full-thickness epidermal necrosis (Figures 3 and 4). The PAS stain failed to reveal any dermatophytes. However, the PAS did reveal normal thickness of the epidermal basement membrane, consistent with fixed drug eruption.

After the biopsy results returned, a careful review of the patient’s medical history revealed that each episode was produced by the same event — recreational use of marijuana. A short course of topical corticosteroid therapy resulted in complete resolution of the lesions, and the patient was advised to abstain from marijuana use.

Discussion
Fixed Drug Eruptions
Drug eruptions are one of the most common cutaneous disorders encountered by dermatologists, representing 2% to 3% of all dermatological issues. FDE is a form of drug allergy that presents as single or multiple round, sharply demarcated, dusky red lesions several centimeters in diameter that occur at the same sites after each administration of the inciting drug. Pruritis and burning are often associated symptoms. The average age of onset is approximately 30 years old, and the most commonly implicated medication is trimethoprim-sulfamethoxazole. Between the time when the individual is first exposed to the medication and development of the first lesion, a variable refractory period can exist, ranging from a week to months or even years. With subsequent exposure, lesions appear within 30 minutes to eight hours. Typically, the lesions heal with residual hyperpigmentation. However, other types of FDE have been reported (Table 1).
Our patient presented with the classic pigmented FDE, with lesions appearing within six hours of marijuana use. While generally only a solitary lesion appears on first exposure, repeated administration of the medication can lead to new lesions or an increase in size of the original lesions. Although they can occur anywhere on the skin, FDE's most commonly occur on the glans penis, lips, palms, soles and groin area. Overall, the legs are most commonly affected in women and the genitalia are most commonly affected in men.

As explained by Pai et al., the reaction “is believed to be a lymphocyte CD8-mediated reaction, wherein the offending drug may induce local reactivation of memory T cell lymphocytes … targeted initially by the viral infection.” Histological examination displays two possible scenarios depending on when the biopsy is done. In lesions that are only one to two days old, examination reveals hydropic degeneration of basal keratinocytes with dyskeratotic cells in the epidermis and exocytosis of mononuclear cells. Healed hyperpigmented lesions often demonstrate pigmented incontinence revealing dermal melanophages with little perivascular infiltration of inflammatory cells, as seen in our patient. To identify the culprit of the FDE, provocation tests can be done, with the patch test being the most commonly used method. The patch test is effective as long as it is placed over a previously involved site and the patient is not in the refractory period. Challenging a patient with an oral provocation test has been associated with generalized bullous lesions in some cases. In our case, we did not re-challenge the patient with the suspected drug due to legal concerns. Treatment consists of cessation of the suspected drug along with the use of topical steroids and systemic antihistamines. Extensive lesions, or those with bullae, may require systemic corticosteroids. Post-inflammatory hyperpigmentation can be treated with hydroquinone bleaching creams.

Cutaneous manifestations of illicit drug use
According to the Substance Abuse and Mental Health Administration, in 2013 “an estimated 24.6 million individuals aged 12 or older were current illicit drug users,” representing over 9% of the population in the United States. Dermatologists may be the first to recognize drug abuse in select patients, allowing for earlier intervention and treatment (Table 2). As often the vascular and cardiac manifestations are internal, they cannot be readily seen by clinicians outside of dermatology.

Cannabis
Cannabis remains the most commonly used illicit drug, with an estimated 7% of the population in the United States using this substance regularly. Since the Neolithic times, cannabis, which is the Latin name for hemp, has been widely used, with the first account of marijuana in the Western medical literature reported in 1840 by the British physician O’Shaughnessy. Today, Cannabis sativa has a wide variety of uses ranging from recreational use for its psychoactive properties to medicinal properties, to biofuel, insulation, animal litter, paper, cosmetics, rope and fabric manufacturing. The stem provides the fibers, while the resin produced from the flowering tops is often used recreationally. The seeds are commonly used for birdseed or fishing bait. There are four subspecies of Cannabis sativa, varying in geographic location and in application (Table 3). “Hashish” refers to the unadulterated resin that is collected and dried, while marijuana refers to the cut flowers, leaves and stems, which generally possess a fifth of the potency of hashish.

Cannabis can be smoked or consumed in foods, infusions or vapor form. Delta-9-tetrahydrocannabinol (THC), the main

Table 1. Types of Fixed Drug Eruptions (FDE) and Examples of Causes

<table>
<thead>
<tr>
<th>FDE Type</th>
<th>Presentation</th>
<th>Known Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pigmenting</td>
<td>Lesions that heal with residual hyperpigmentation</td>
<td>Barbiturates, penicillin, NSAIDs sulfonamides, tetracyclines, bismuth, iodosides</td>
</tr>
<tr>
<td>Erythema multiforme-like</td>
<td>Lesion with three zones: central, dusky purpura; elevated, edematous, pale ring; and surrounding erythema</td>
<td>Mefamic acid20</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis-like</td>
<td>Widespread, bullous lesions</td>
<td>NSAIDs21</td>
</tr>
<tr>
<td>Linear</td>
<td>Multiple lesions that are distributed linearly; may follow Blascho’s lines or nerve-root distribution</td>
<td>Trimethoprims</td>
</tr>
<tr>
<td>Wandering</td>
<td>Involved sites that don’t flare with each exposure and activity that does not always appear at the same location with each recurrence</td>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Nonpigmenting</td>
<td>Lesions that do not leave any residual hyperpigmentation and appear uniformly red</td>
<td>Pseudoephedrine hydrochloride, tetrahydrozoline, contrast media, beta-histine, etodolac</td>
</tr>
<tr>
<td>Bullous</td>
<td>Subepidermal blisters that heal without scarring</td>
<td>Aminophenazon, antipyrine, barbiturates, cotrimoxazole, trimethoprims, sulfamethoxazole, diazepam, mefenamic acid, acetaminophen, phenylbutazone, piroxicam, sulfadiazine, sulfathiazole</td>
</tr>
</tbody>
</table>

Table 2: Cutaneous manifestations of illicit drug use

<table>
<thead>
<tr>
<th>Illicit Drug</th>
<th>Percent of Americans Using (12+ Years Old)</th>
<th>Cutaneous Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis</td>
<td>7.5%</td>
<td>Contact urticaria, cannabis arachnitis, skin aging</td>
</tr>
<tr>
<td>Cocaine/Crack</td>
<td>0.6%</td>
<td>Nasal septal perforation, “snorter warts,” madarosis, bullous erythema multiforme, “crack hands,” scleroderma, Henoch-Schonlein purpura, vasculitis due to levamisole</td>
</tr>
<tr>
<td>Ecstasy</td>
<td>0.4% hallucinogen use (including LSD and ecstasy)</td>
<td>“Ecstasy pimples,” guttate psoriasis</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>0.2%</td>
<td>“Meth mites,” “meth mouth,” xerosis, premature aging</td>
</tr>
<tr>
<td>Heroin</td>
<td>0.1%</td>
<td>Track marks, cellulitis, candida folliculitis, transcutaneous botulism, granuloma formation, pruritis, fixed drug eruption, “puffy hand syndrome,” tourniquet hyperpigmentation</td>
</tr>
</tbody>
</table>
psychoactive substance in cannabis, which is found in the plant's resin, is responsible for its perception- and mood-altering properties. The concentration of THC can vary from 0.1 to 12%, depending upon the subspecies and method of preparation. The onset of activity after smoking marijuana is within 10 to 20 minutes, and the effects usually resolve within three hours. Cutaneous manifestations of marijuana present as conjunctival injection, contact urticaria, and type 1 hypersensitivity, which can include anaphylaxis or cannabis arteritis. Cannabis arteritis, a subtype of thromboangiitis obliterans, is seen mainly in long-term users. Cannabis arteritis is believed to be caused by the vasoconstrictive side effects of THC and contaminants such as arsenic (known to cause thromboangiitis obliterans in cigarette smokers) and is one of the major causes of peripheral arterial disease in patients under the age of 50. Manifestations of this atherosclerosis include Raynaud’s phenomenon; digital necrosis with small, dry necrotic patches on the extremities; and decreased tibial and pedal pulses. Diagnosis is based upon duplex ultrasound in order to differentiate it from atherosclerosis. Treatment includes cessation of marijuana, aspirin (81 mg to 200 mg daily) or, in severe cases, iloprost. Smoking marijuana is also associated with premature skin aging, resulting in prominent wrinkles. A case of erythema multiforme-like recurrent drug eruption was also reported with marijuana use. No reported cases of fixed drug eruption secondary to marijuana use were found in a literature search.

In the 1980s, an epidemic of fixed drug eruptions occurred in Holland due to heroin being smoked, and presented as hyperpigmented lesions of the tongue. Despite denial by our patient, one possibility is that heroin may have been mixed in the marijuana cigarette, and thus the FDE may have been due to adulterants and not the marijuana.

Conclusion

To our knowledge, this is the first case report describing fixed drug eruption elicited by recreational marijuana use. With 19.8 million current users in the United States and the growing rate of use associated with legislature changes, questions regarding a patient's recreational drug use should be included in the patient's history. By recognizing the cutaneous findings of illicit drug use, dermatologist can stand on the forefront of early recognition.

Table 3: Subspecies of Cannabis sativa

<table>
<thead>
<tr>
<th>Cannabis sativa Subspecies</th>
<th>Use</th>
<th>Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sativa (cultivated hemp)</td>
<td>Recreational (high THC content), industrial uses</td>
<td>Worldwide, primarily equatorial regions</td>
</tr>
<tr>
<td>Indica (Indian hemp)</td>
<td>Recreational use (high THC content), seldom used for its fiber</td>
<td>Himalayas, Middle East, India</td>
</tr>
<tr>
<td>Spontanea (wild hemp)</td>
<td>Industrial use (low THC content, not commonly used for recreation)</td>
<td>Eastern Europe, China, Russia</td>
</tr>
<tr>
<td>Kafiristanica (Afghan hemp)</td>
<td>Recreational use (high THC content), unfit for manufacturing of fibers</td>
<td>Afghanistan, Pakistan</td>
</tr>
</tbody>
</table>

References

8. Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. The NSDUH Report: Substance Use and Mental Health Estimates from the 2013 National Survey on Drug Use and Health: Overview of Findings. SAMHSA: Rockville (MD); 2014.

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Abstract

Bullous congenital ichthyosiform erythroderma is a rare genodermatosis that affects 1 in 200,000 people. Management for adults entails symptomatic relief, but infants may require intensive care if substantial blistering is present. We present a case of bullous congenital ichthyosiform erythroderma in a 48-year-old male and provide a discussion about the disease and treatment options.

Introduction

Bullous congenital ichthyosiform erythroderma (BCIE) is a rare genodermatosis that was formerly known as epidermolytic hyperkeratosis (EHK) or epidermolytic ichthyosis (EI). About 50% of cases arise from spontaneous mutation, but autosomal-dominant (AD) and rare autosomal-recessive forms also exist.1-3 BCIE clinically manifests with erythema, blistering, and erythroderma in infancy, but the severity of disease may decrease over time.1

Case Report

A 48-year-old African American male presented for evaluation of blisters and scaling over the entirety of his body since birth. The blisters were painful, pruritic, and made worse by heat and sweating. He had previously used Eucerin lotion without relief. The patient had an otherwise unremarkable 12-point review of symptoms except for mild joint pain, 15 pack-year smoking history, and moderate alcohol intake.

Dermatological examination revealed marked hyperkeratosis, thickened palms with palmoplantar keratoderma, hyperlinear creases, and soles with fissures and cracks (Figure 1). Brown, cardboard-like scale with desquamation on the neck, back, abdomen, and extremities was also present. The lesions extended to the volar aspect of the wrists, the dorsa of the feet, and the Achilles tendon. Dark-brown hyperkeratosis with mild scaling, arrayed in a linear fashion, was present in his axillae, antecubital fossa (Figure 2), and popliteal fossa. Brown, cardboard-like scale with desquamation on the neck, back, abdomen, and extremities was also present. The lesions extended to the volar aspect of the wrists, the dorsa of the feet, and the Achilles tendon. Dark-brown hyperkeratosis with mild scaling, arrayed in a linear fashion, was present in his axillae, antecubital fossa (Figure 2), and popliteal fossa.

Fig 1. Thickened palm with palmoplantar keratoderma and hyperlinear creases

Fig 2. Antecubital fossa with dark-brown hyperkeratosis and scaling

There were also few coarse, irregularly shaped, keratohyalin granules and intracytoplasmic vacuolization, along with involvement of the entire suprabasal layer. This was consistent with the diagnosis of BCIE.

Fig 3. Orthokeratotic hyperkeratosis, hypergranulosis, church-spire-like papillomatosis, and marked vacuolar changes in the keratinocytes of the upper spinous and granular layers (H&E, 40x)

Discussion

BCIE is a rare AD genodermatosis that was first described by Brocq in 1902.4 It is caused by mutations in keratin 1 and keratin 10 that impair intermediate filament formation in the suprabasal keratinocytes, although a case with a novel mutation in the 1A helix initiation motif of keratin 1 has been reported.4 Confirmation of disease can be established by mutation-specific testing for keratin defects using buccal swabs or blood.5 Cost constraints prohibited genetic testing and genetic counseling for our patient, but these services should be offered to affected individuals and families. Patients should also be made aware of the possibility of passing the chromosomal defect on to their children.

Clinically, BCIE presents in neonates with erythema, widespread superficial blistering, and erythroderma. If the blisters rupture, they may leave raw, denuded areas that can cause secondary infections, sepsis, dehydration, electrolyte imbalances, and hypothermia. In light of these concerns, affected newborns should be handled gently and transferred to the intensive care unit (ICU) immediately after birth. Although a
References


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Proteus Syndrome: Case Report and Review

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Abstract
Proteus syndrome (PS) is a rare, progressive hamartomatous disorder characterized by overgrowth and hyperplasia of diverse tissues including connective tissue, bone, skin, adipose, and central nervous system. Mosaic expression of a post-zygotic somatic mutation in the AKT1 gene results in random distribution of affected tissues and creates significant phenotypic variability among patients. Herein, we describe a case of PS presenting with a cerebriform connective-tissue nevus in a 14-year-old male and review the pathogenesis, clinical presentation and differential diagnosis, management, and prognosis of patients with the disorder.

Introduction
Proteus syndrome was first described in 1979 by Cohen and Hayden, and it was named by Weidmann et al. in 1983 for the Greek god Proteus, who was capable of assuming many forms. With fewer than 100 confirmed cases reported, Proteus syndrome is extremely rare; its estimated incidence is less than 1:1,000,000 persons. It is seen twice as frequently in males, and there is no ethnic predilection. The variable presentation and rarity of the disease led to frequent misdiagnosis of the disorder until 1999, when Biesecker et al. proposed detailed and specific diagnostic criteria.

Case Presentation
A 14-year-old Caucasian male presented with a slowly enlarging growth on the bottom of his left foot that was present for about three years. The patient reported some discomfort with ambulation due to the increasing size of the lesion. His medical history included chronic macrocytosis and reticulocytopenia, which prompted a bone marrow biopsy at the age of 10. No evidence of hematologic malignancy was found; however, a non-clonal chromosome 15 deletion: 45 XY del(15)(q11.2) was revealed. (Chromosome 15 deletions have been described in association with myelodysplastic syndrome.) The patient also had a history of developmental abnormalities and was diagnosed with autism/Asperger’s disease. An MRI of the brain from five years prior revealed encephalomalacia and periventricular leukomalacia (localized areas of necrosis attributed to infarction or ischemia). One of the patient’s two brothers had spina bifida.

A full skin examination revealed one café au lait macule on the back. The plantar aspect of the left foot contained several flesh-colored cerebriform papules and nodules (Figure 1). Partial biopsy of the lesion was performed. Histology revealed dense connective tissue beneath an acanthotic, acantholytic epidermis. Stellate cells and entrapped adipose tissue were present in the dermis (Figures 2a [2x], 2b [10x]). The patient was assigned a diagnosis of Proteus syndrome and referred for genetic testing.

Pathogenesis
Proteus syndrome is a progressive, hamartomatous disorder that may involve any germ layer. The hypothesized pathogenesis involves a post-zygotic somatic mutation in the AKT1 gene (chromosome 14q32.33), which is lethal in the non-mosaic state. This gene belongs to the AKT family of serine/threonine kinases and is involved in regulation of multiple cellular processes, including proliferation and survival, cell size and response to nutrient availability, tissue invasion and angiogenesis. Constitutive activation of the protein underlies the overgrowth and tumor susceptibility in patients carrying this mutation. Mosaic expression of the mutation is what results in the random distribution of affected tissue and creates significant phenotypic variability among patients. Accordingly, an early post-zygotic mutation results in a greater number of disease manifestations than a late mutation, because the early somatic cell carrying a mutation would give rise to more affected cell lineages.

Due to the clinical overlap with other hamartomatous disorders, a mutation in the tumor suppressor gene PTEN was initially thought to be pathogenic in PS. However, it is now believed that individuals with PTEN gene mutations and asymmetric overgrowth do not meet the diagnostic criteria for Proteus syndrome. Instead, these individuals are considered part of a larger group of disorders called PTEN hamartoma tumor syndromes. Other entities in this group include Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus-like syndrome. AKT1 is activated by loss-of-function mutations in PTEN, which explains why patients with such mutations and those with activating mutations in AKT1 display overlapping clinical features.

Clinical Manifestations
The clinical features of PS arise postnatally with irregular, asymmetric, progressive overgrowth that can involve many tissues, most commonly bone, connective tissue and fat. Skeletal changes include gigantism of the hands and/or feet and partial or complete hemihypertrophy. Localized overgrowths may exert asymmetric forces on the spine and result in scoliosis. Connective-tissue abnormalities, such as cerebriform connective-tissue nevi (CCTN), typically present in the first or second year of life and tend to evolve slowly, in some patients continuing to develop throughout adolescence. The lesion is virtually pathognomonic for PS and appears as gyriform gross thickenings of cutaneous and subcutaneous tissues, most commonly on the soles and occasionally on the hands, abdomen, and nose.

Other dermatological manifestations include linear verrucous epidermal nevus, which tend to develop in the first year of life, and vascular malformations that can be either venous, capillary, lymphatic-type, or mixed. Four types of abnormalities of fat may occur in Proteus syndrome: (1) lipomas, (2) lipohypoplasia, (3) fatty overgrowth, and (4) localized fat deposits or partial lipohypoplasia. Lipomas may be single or multiple and occur subcutaneously or internally. Lipomas of the abdomen and thorax can be very aggressive despite their benign histology.

Specific facial features have been described in...
patients with PS and are most commonly seen in individuals with cognitive deficits. These include down-slaning palpebral fissures, flattening of the malar bones, a relative lengthening of the face, low nasal bridge with wide nostrils, and a persistently open mouth.3 Our patient did not display any of these characteristics.

Central nervous system abnormalities are seen in up to 40% of patients with PS.4 Dietrich et al. described 12 children with PS whose CNS abnormalities included hemimegalencephaly (8), hypodense periventricular white matter (4), periventricular calcification (3), corpus callosal abnormalities (3), atrophic brains (2), and Dandy-Walker malformation (1).5 Mental deficiency is seen in approximately 30% of cases.3

While no specific hematologic abnormalities have been described in association with PS, studies have demonstrated that AKT1 and AKT2 are critical regulators of long-term hematopoietic stem-cell function.6 It is feasible that an AKT1 gene mutation may underlie the chronic macrocytosis and reticulocytopenia observed in our patient.

Patients with PS are prone to developing several types of tumors, most commonly monomorphic adenomas of the parotid gland, ovarian cystadenomas, meningiomas, and various types of testicular tumors.7 Cystic lung disease may cause pulmonary insufficiency, persistent atelectasis, pneumonia, or even death.3

Other manifestations include ophthalmologic findings such as strabismus, epibulbar cysts, and epibulbar dermoids (42%); otolaryngologic abnormalities (37%); mental deficiency (30%); non-cticus pulmonary disease (20%); dental abnormalities (19%); reproductive/genital non-tumor abnormalities (18%); male reproductive tumors (11%) and renal/urologic manifestations (9%); and hair and nail abnormalities.7

**Diagnosis**

The diagnosis of Proteus syndrome is based on clinical findings. Individuals must meet all of the general criteria, including mosaic distribution of lesions, sporadic occurrence, and progressive course, along with certain specific criteria as outlined in Table 1.

Although PS is primarily a clinical diagnosis, molecular genetic testing for the somatic mutation in the AKT1 gene can be helpful to confirm the diagnosis. This can be technically challenging because blood is not an appropriate source and tissue may show low-level mosaicism. Skin scrapings from epidermal nevi in PS patients have been shown to be a good source of mutant cells and may provide an alternate source for genetic testing.8 It is important to note that PS is not inherited, so prenatal testing is not indicated.

**Differential Diagnosis**

Among the differential diagnoses for Proteus syndrome are those entities described as part of PTEN hamartoma tumor syndrome. Bannayan-Riley-Ruvalcaba syndrome is an autosomal-dominant disorder characterized by macrocephaly, angiomatosis, lipomatosis, polyposis of the colon and rectum, and pigmented macules of the penis. These patients lack the progressive digital overgrowth, skull exostoses, epidermal nevi, and palmar or plantar changes seen in Proteus syndrome. Patients with Cowden syndrome typically present with facial trichilemmomas, acral keratoses, papillomatous lesions, lipomas, hemangiomas, and epidermal nevi (Cowden nevus), but do not develop cerebriform connective-tissue nevi. These patients also carry an increased risk for breast, thyroid, and endometrial cancers. Patients with Proteus-like syndrome have significant clinical features of PS but do not meet the diagnostic criteria for PS. They are distinguished by macrocephaly, marked lipohypertrophy, and lack of progressive bony overgrowth.

In SOLAMEN (segmental overgrowth, lipomatosis, AVs, epidermal nevus) syndrome, patients display thickening of the soles and increased wrinkling instead of the gyri found in CCTN. There is segmental proportionate overgrowth with soft-tissue hypertrophy and ballooning effect, as well as lymphatic and shunting arteriovenous malformations.12 Proteus syndrome may be distinguished from neurofibromatosis by the absence of multiple café au lait macules, Lisch nodules, axillary freckling, and multiple neurofibromas. Hemihyperplasia and multiple lipomatosis syndrome (HHIML) is characterized by subcutaneous lipomatosis and asymmetric overgrowth (hemihyperplasia) that is not as progressive as in PS.3

Syndromes characterized by vascular malformations may also be considered in the differential diagnosis of PS. In Maffucci syndrome, enchondromatosis, most commonly of the hands and feet, with multiple cavernous hemangiomas are seen.13 This should not be difficult to distinguish from Proteus syndrome owing to the lack of enchondromatosis in Proteus syndrome. Klippel-Trenaunay syndrome is characterized by the three main features of nevus flammeus (port-wine stain), venous and lymphatic malformations, and soft-tissue hypertrophy of the affected limb. There are no CCTN seen, and overgrowth is present at birth and more severe than in PS.14 In Parkes Weber, a mutation in the RASA1 gene leads to multiple capillary malformations, including AV fistulas that can lead to heart failure, as well as overgrowth of one limb, most commonly the leg.15 In the differential diagnosis of the CCTN is isolated plantar collagenoma, a hamartomatous lesion consisting of proliferation of normal collagen tissue.16 Collagenomas are commonly encountered in other genetic disorders, such as Buschke-Ollendorff syndrome, a rare autosomal-dominant condition, resulting from nonsense mutation in the LEMD3 gene, which encodes for a potent negative regulator of bone morphogenetic protein and transforming growth factor-β signaling pathways. Recently,
a mutation in LEMD3 has been reported in familial cutaneous collagenomas as well.14

Histopathology
Histopathologically, cerebriform connective-tissue nevi are characterized by an irregular proliferation of highly collagenized fibrous tissue.15 Biopsies of lipomatous overgrowths reveal nonencapsulated lobules and mature adipocytes.16 Vascular malformations are lined by flat endothelium, exhibiting a normal, slow rate of turnover. The flat, organoid type of epidermal nevus in PS shows acanthosis, hyperkeratosis, and a mutation in skin scrapings from epidermal nevi enables non-invasive molecular diagnosis in patients with Proteus syndrome. Am J Med Genet. 2013;161A:889–891.

Management
The sporadic and unpredictable nature of Proteus syndrome can pose a challenge for health care providers. Since PS can affect many different parts of the body to varying degrees, a multidisciplinary approach is important in the management and prevention of secondary complications. Serial clinical photography with an initial skeletal survey and targeted follow-up radiographs should be performed to evaluate the degree of obstruction or deformation based on the patient’s medical history and physical exam.18 Other imaging recommendations include intracranial MRI to evaluate for CNS malformations that may be associated with developmental delay, mental retardation or seizures. Findings may include multiple meningiomas, polymicrogyria, and periventricular heterotopias.3 Abdominal MRI is recommended to exclude intra-abdominal lipomas, regardless of the presence of symptoms, due to the aggressive nature of these lesions. CT of the chest to evaluate pulmonary cystic malformations should be carried out if clinically warranted to evaluate for cystic malformations.3

One of the most common causes of death for patients with PS, including children, is deep venous thrombosis and pulmonary embolism. For this reason, perioperative anticoagulant is recommended.18 Chronic anticoagulation, however, is not recommended, particularly since many of these patients have underlying vascular anomalies. Tumor surveillance is not recommended in PS patients. These patients appear to be predisposed to a broad range of malignancies, and it has not been demonstrated that early detection of tumors in PS improves prognosis.18

Cerebriform connective-tissue nevus (CCTN) is a common dermatologic overgrowth that is usually found at the plantar aspect of the foot. The grooves in CCTN can be difficult to clean, leading to the accumulation of bacteria and fungus that may cause infection and a malodor. CCTN can progressively increase in size, grow on previously non-involved areas of the foot and coalesce. This can be disfiguring, painful, and interfere with ambulation.3 Surgical removal of CCTN can lead to disappointing results since recurrence and painful scarring is possible.39 Dermatological follow-ups and the use of custom orthotics to manage pain, pressure ulcers, and/or skin breakdown are preferred treatments.3,16 Because patients and their families can undergo a great deal of stress from this disease, clinicians are encouraged to assess psychosocial issues routinely with parents and children and refer for counseling and peer-support groups if needed.20

Prognosis
Regarding progression of skin lesions, Beachkofsky et al. evaluated 36 patients with Proteus syndrome with serial photography for an average of 53 months. Cerebriform connective-tissue nevi showed progression in 13 children but not in 3 adults. Lesions progressed by expansion into previously uninvolved skin, increased thickness, and development of new lesions. Lipomas increased in size and/or number in 8 out of 10 children. Epidermal nevi and vascular malformations generally did not spread or increase in number.21

Long-term prognosis varies across patients. Approximately 20% of PS patients suffer premature death, most commonly due to venous or pulmonary thromboembolism, pneumonia, or surgical complications.4,22

Conclusion
Proteus syndrome is a complex disease that can involve many areas of the body, especially the skeletal system, connective tissue, fat, and central nervous system. The variable clinical presentation, rarity of the disorder, and clinical overlap with several other diseases has led to significant confusion and misdiagnosis. Molecular genetic testing can be performed, with the highest yield from epidermal nevi or tissue specimens. Patients should be managed with a multidisciplinary approach.

References
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Reactive Keratoacanthoma Responding to Excision and Healing by Secondary Intention

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Abstract
Keratoacanthomas (KA) are rapidly-growing tumors of uncertain etiology. KAs mimic squamous-cell carcinoma (SCC) histologically but have the capacity to regress spontaneously or, rarely, progress to metastatic SCC. KA recurrence has been noted following complete excision and destructive treatment modalities. The term "reactive KA" has been used in this setting. We report three cases of reactive KAs that responded to excision and healing with secondary intention.

Introduction
While the pathogenesis of keratoacanthoma (KA) development is debated and likely multifactorial, KA formation at sites of cutaneous trauma are well-documented in the literature. The term "reactive KA" has been used in this setting. In reviewing the literature, the time from treatment to appearance of reactive KA ranges from two weeks to six months, with a mean of two months. Most patients are elderly, with a mean age of 80, and most reactive KAs occur on exposed areas of the extremities. We report three cases of reactive KA effectively treated with surgical excision utilizing minimal cutaneous trauma.

Case 1
A 57-year-old woman with a history of numerous SCCs on the bilateral dorsal forearms presented for evaluation of two hyperkeratotic nodules on the right forearm (Figure 1A). Biopsies confirmed well-differentiated SCCs (Figure 1B). Both were completely excised, and the defects closed primarily. She returned five weeks later for evaluation of hyperkeratotic plaques involving both previous excision scars and a new nodule on the mid forearm. Biopsy of all three lesions

Figure 2. (A) Shave with excoriation and features of lichen simplex chronicus with tongues and lobules of atypical keratinocytes extending to biopsy base (H&E, 4x). (B) Lesions treated with IL bleomycin or triamcinolone. (C) No recurrence at follow-up.
showed well-differentiated SCC. The largest lesion was re-excised and closed primarily. She returned five weeks later for treatment of the remaining SCCs, and a new nodule was noted in the recent re-excision scar (Figure 1C). Reactive KAs were suspected, and all three lesions on the right forearm were excised and left to heal by secondary intention. Histology confirmed well-differentiated SCC with clear surgical margins (Figure 1D). The patient returned four weeks later with three new hyperkeratotic nodules involving the remainder of the scar on the right lower forearm. Histology revealed excoriated atypical squamous proliferations (Figure 2A). All three nodules were treated with 0.2 cc intralesional bleomycin (1 unit/cc). Additional nodules developing in previous saucerization scars were biopsied and found to represent hypertrophic scars, which were injected with 1% triamcinolone (Figure 2B). The patient has shown no evidence of recurrence after six months of follow-up (Figure 2C).

**Case 2**

An 81-year-old man presented for re-excision of a recurrent SCC on the left elbow (Figure 3A). The lesion had been previously excised three times over an eight-month period. The SCC was removed with two stages of Mohs micrographic surgery (MMS), and the defect was closed primarily. The patient returned four weeks later with two hyperkeratotic nodules within the excision scar (Figure 3B). Biopsy revealed a squamous proliferation with features of KA (Figure 3C). Reactive KA was suspected, and the nodules were excised utilizing minimal electrocautery and the defect left to heal by secondary intention. There has been no evidence of recurrence after 18 months of follow-up.

**Case 3**

A 76-year-old woman presented with a rapidly-enlarging nodule on the left upper pre-tibia. She had a history of two previous SCCs excised from that leg without complication. Biopsy revealed SCC. The lesion was excised with one stage of MMS and repaired with primary closure. Four months later she returned with a nodule developing in the center of the scar (Figure 4A). Biopsy showed an invasive, well-differentiated SCC (Figure 4B). Reactive KA was suspected, and the lesion was excised with the defect allowed to heal by secondary intention. One vein was ligated with 4-0 polyglactin 910 suture, and no electrodessication was used. There has been no evidence of recurrence after six months of follow-up.

**Discussion**

The pathogenesis of KA development is likely multifactorial. Genetic predisposition, immunosuppression, ultraviolet (UV) radiation, chemical carcinogens, and viral infections have all been implicated. KA formation at sites of thermal burns, laser resurfacing, chemical peels, skin graft donor sites, and other forms of cutaneous trauma has been documented. KA recurrence following routine surgical excision occurs at a rate of 4% to 8%, though this does not appear to denote increased malignant behavior. Brisk KA recurrence has been documented following histologically confirmed complete excision and MMS. The term “reactive KA” has been used in this setting. In reviewing the literature, the time from treatment to appearance of reactive KA ranges from two weeks to six months, with a mean of two months. Most patients are elderly, with a mean age of 80, and most reactive KAs occur on exposed areas of the extremities.

Distinguishing between a recurrent, incompletely excised SCC and a reactive KA is a subject of debate. A true recurrence would be expected to develop in the most central aspect of a scar. Some of the lesions we encountered occurred on the lateral aspect of excision scars, which suggests the lesions were instead reactive in nature. Additionally, the rapid timing of recurrence supports this etiology.

The dilemma is further compounded by indistinct histologic features. It is not possible to distinguish reactive KAs histologically. A well-differentiated SCC with endophytic or crateriform features mimics KA both in architecture and sometimes in cytology with the classic description of keratinocytes at the periphery exhibiting glassy eosinophilic cytoplasm. However, most reactive KAs seem to have the helpful feature of being associated with the infundibular portion of one or more hair follicles. KAs are thought to arise from...
folicular infundibula in hair-bearing (most often exposed) skin. It is also possible that although the natural history of a KA results in spontaneous involution, a bona fide SCC might arise within a lesion of KA.

It has been proposed that surgical trauma, including the use of electrodessication and placement of sutures, can contribute to the formation of reactive KAs, possibly representing a form of Koebner phenomenon. Minimizing surgical trauma led to resolution of several recrudescent reactive KAs in our case series. Needle puncture sites should also be minimized during anesthesia administration.

We report one patient who developed several lesions that responded to IL bleomycin. Intralesional 5-FU and methotrexate are other non-surgical treatment modalities that have been reported to be successful for reactive KAs. Systemic retinoids such as acitretin have also been effective in maintaining lesion clearance. Destructive modalities such as electrodessication and curettage (ED&C) and external beam radiation have been associated with worsening of the condition.

**Conclusion**

Early recognition of the reactive KA phenomenon is important in order to prevent disfigurement and morbidity to the patient. In our series, the reactive KAs were excised, and particular effort was made to minimize electrodessication and suture placement. This approach was effective for all lesions treated.

**References**


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A Case of Cutaneous Rosai-Dorfman Disease

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Abstract

Rosai-Dorfman disease (RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML), is a benign, self-limiting disease of histiocytes with unknown etiology. RDD typically presents in the first or second decade of life with massive, painless cervical lymphadenopathy. Cutaneous RDD is a rare, extra-nodal variant that is strictly limited to the skin. In both forms, the histiocytes stain positive for S-100 protein and negative for CD1a. Herein, we describe a rare case of cutaneous RDD presenting on the face and trunk of a 79-year-old man and review the literature on systemic RDD and its rare cutaneous variant.

Introduction

Systemic Rosai-Dorfman disease (S-RDD), also known as sinus histiocytosis with massive lymphadenopathy (SHML), is a non-Langerhans cell histiocytosis first recognized as a distinct clinicopathologic entity by Rosai and Dorfman in 1969.1 It commonly presents as bilateral, painless cervical lymphadenopathy with fever, leukocytosis, anemia, elevated erythrocyte sedimentation rate, and polyclonal hypergammaglobulinemia.1,2 Although less common, other lymph nodes may be involved.2 Lymphadenopathy with extranodal disease may occur in up to 43% of patients and includes sites on the skin, soft tissues, eyes, respiratory tract, liver, spleen, testes, skeleton and nervous system.2,3 Purely extranodal cutaneous disease without lymph node involvement is rare. Herein, we describe a rare case of cutaneous RDD without lymph node involvement in a 79-year-old man.

Case Report

A 79-year-old male with no significant past medical history presented to our dermatology clinic with multiple, asymptomatic lesions on his face and trunk of two years’ duration. Physical examination revealed violaceous papules and nodules on his cheek, chest and upper back (Figures 1a - 1c). No other lesions were noted, and no lymphadenopathy was appreciated. He denied any history of fever, weight loss, night sweats, or malaise. His complete blood cell count, complete metabolic panel, antinuclear antibody, serum protein electrophoresis, and urine protein electrophoresis were all within normal limits. Erythrocyte sedimentation rate was slightly elevated at 21 mm/hr.

A skin biopsy of two lesions was performed, and histopathological examination revealed a diffuse, predominantly histiocytic dermal infiltrate with a background of small lymphocytes, neutrophils, and scattered plasma cells (Figure 2). A number of histiocytes showed emperipolesis (Figure 3). Immunohistochemical staining was positive for S-100 protein (Figure 4) and CD68, and negative for CD1a. Based upon clinicopathological correlation, a diagnosis of cutaneous Rosai-Dorfman disease was made, and the patient was referred to oncology for workup of systemic involvement.

Discussion

S-RDD, or sinus histiocytosis with massive lymphadenopathy, is a rare disorder characterized by a proliferation of non-Langerhans cell histiocytes in the lymph node. It may have extranodal involvement, the skin being the most common site. RDD limited to the skin without nodal involvement, or cutaneous Rosai-Dorfman disease (C-RDD), is even rarer, with only 85 cases having been described.4,5 Contrary to the systemic form, C-RDD generally has no systemic involvement or laboratory abnormalities.4,5 Clinically, the cutaneous lesions are similar in both S-RDD and C-RDD. The lesions are often slow-growing, asymptomatic papules and nodules with yellow to red, brown, or violaceous color, varying in size from less than 1 cm to 30 cm.4,6,8 The lesions may be localized or disseminated.4,5 C-RDD tends to occur in slightly older age groups, in women, and in non-black ethnic groups, in contrast to the systemic form, which affects children and young adults in the first or second decade of life.1,2,4,6

The etiology of S-RDD and C-RDD remains unclear, and a debate between infection, immune dysregulation, and neoplasia remains.2,4,9 To date, many infectious agents, including Epstein-Barr virus, human herpesvirus 6, Brucella, Klebsiella rhinoscleroma and many others, have been reported in association with RDD.2 In addition, autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and thyroid disease have been associated with RDD.4,5 Histopathologically, systemic and cutaneous RDD are indistinguishable. The main microscopic findings include proliferation of large polygonal and palely eosinophilic histiocytes with variable amounts of a mixed, but predominantly chronic, inflammatory infiltrate. Emperipolesis is often present, which is the intracytoplasmic inclusion of inflammatory cells including lymphocytes, plasma cells, and neutrophils within vacuoles.4,6,8 The cells are also characterized by round or oval vesicular nuclei.2,4,8,9 The pattern of the infiltrate in cutaneous layers is usually nodular and diffuse but may be patchy or interstitial and correlates with the clinical presentation.4,8 The infiltrate is mostly confined to the dermis but may have some subcutis involvement or be confined to only the subcutis.4,8 Epidermal changes are usually absent or mild.4,8 The histiocytes stain positive for S-100 protein and negative for CD1a, unlike the Langerhans cells, which stain positive for both markers.4,8

Figures 1a - 1c: Violaceous papulonodular lesions on the left cheek, chest, and back.
Both S-RDD and C-RDD generally have a benign course with spontaneous regression over a period of months to years, although a small number of patients may have significant morbidity, directly or indirectly from the disease. Due to S-RDD having lesions in any organ system, complications are more common with S-RDD than C-RDD. Treatment of RDD is based on anecdotal reports, and several therapies have been utilized with variable rates of success, including glucocorticoids and chemotherapy for S-RDD.

C-RDD is benign and usually self-limited. Documented treatments of C-RDD include surgical excision, glucocorticoids, antibiotics, cryotherapy, radiotherapy, thalidomide, isotretinoin, acitretin, interferon-alpha, dapsone, methotrexate, and pulsed dye laser, with surgery yielding the highest success rates.4,5

Conclusion
Due to the rarity of C-RDD, insufficient data and studies of small sample sizes fail to clarify whether C-RDD is a specific subset of S-RDD, a separate entity, or if the two are part of a spectrum. The pathogenesis of RDD remains largely unknown. Although studies do not support progression of C-RDD to S-RDD, long-term follow-up is nonetheless recommended to rule out systemic involvement and associated autoimmune and neoplastic diseases.4-7 Our patient had only skin involvement with no adenopathy or systemic involvement. His lesions were controlled with topical mid-potency glucocorticoid.

References
Figure 1. Pruritus

Abstract

Phototherapy is an efficacious method for managing many cutaneous conditions. Although psoriasis is the most commonly treated condition, phototherapy also has a role in the management of pruritic disorders, including atopic dermatitis (AD), prurigo nodularis (PN), and uremic pruritus (UP). We have reviewed the pathogenesis of pruritus and the mechanism of action of phototherapy in treating pruritic disorders. AD is an inflammatory skin condition with an induction of pruritus due to cytokines released by CD4-positive T helper (Th) 2 cells. Langerhans cells, T cells, proinflammatory cytokines, and keratinocytes are decreased in AD patients treated with phototherapy. PN has an increase in mast cells and neuropeptides that mediate pruritus. UV light decreases the release of these neuropeptides and alleviates pruritus in PN. Finally, UP causes a microinflammatory state with changes in cutaneous nociceptive endings. A circulating substance responsible for pruritus in UP is annihilated through the apoptotic actions of phototherapy.

Discussion

Pathogenesis of Itch: Localized itch involves alpha-delta fibers, whereas diffuse, generalized itch is transmitted through dermal unmyelinated c-fibers. Both of these nociceptive fibers travel to the dorsal horn of the spinal cord, which is then processed by the cerebral cortex through the spinothalamic tract. They have a slow conduction velocity and innervate large areas of the skin. Dry skin and disruption of the skin barrier can induce keratinocytes to release pruritogenic substances. Nerve fibers typically end at the dermal-epidermal junction, although some project into the epidermis. Itch receptors, formed mostly by keratinocytes, respond to...
pruritogens such as histamine, proteases, growth factors, neuropeptides, cytokines, and opioids (Figure 1). They are found only in skin, mucus membranes, and cornea. Substance P (SubP) and calcitonin gene-related peptide (CGRP) are the most studied neurotransmitters and have both central and peripheral activity. Allokinesis, the perception of non-pruritic stimuli as pruritic, is due to central sensitization. This explains the intense pruritus AD patients experience in response to sweat or sudden changes in ambient temperature.

Mast cells produce two proteinases, trypthase and chymase. Tryphtase activates C fibers and thus stimulates the sensation of itch. It also triggers the release of SubP, which not only causes pruritus but also evokes further mast-cell activation. Increased levels of trypthase have been observed in patients with UP. The sensations of pain and itch are carried by different C-fibers. Frequency of the stimulus can modulate the magnitude of itch but does not change the quality of itch into pain. Histamine-induced itch activates some motor areas, suggesting a neuronal association between itch and scratching. Scratching and vibration are transmitted by larger A-beta fibers that inhibit itch signals on the slower C-fibers. While pain causes one to avoid a motor response, itch causes a stimulatory motor response. Painful stimuli can inhibit itch, as observed in pruritic patients who only stop scratching once skin lesions begin bleeding and become painful. Itch and pain share the same cortical brain areas but have different patterns of activation: Itch has a weaker activation of somatosensory cortices and a stronger activation of ipsilateral motor areas compared with pain processing.

ATOPIC DERMATITIS (AD)

Pathogenesis of AD: The pathogenesis of AD is a complex interplay between several different cell types and factors. CD-4 positive Th2 cells have been found to play a major role in pruritus induction by producing and releasing cytokines and chemokines. Localization to the skin in AD is due to the presence of a skin-homing receptor on memory effector T lymphocytes, called “cutaneous lymphocyte-associated antigen,” which interacts with the vascular endothelial-cell-surface antigens to direct circulating T lymphocytes to the reactive skin site. Th1 cells initiated by IL-12 predominantly secrete IL-2 and interferon-γ (IFN-γ), whereas Th2 cells are activated by IL-10 to produce mainly IL-4, IL-5, and IL-13. Th2 cells initiated by IL-12 predominantly secrete IL-4, IL-5, and IL-13 than normal skin. The mRNA expression of IFN-γ, however, is similar to that of normal skin. Chronic lesions express more IL-5, IL-12, and anti-IL-4 p55 protein (ECP) antibody eosinophils than acute lesions. Thus, IL-12 may be important in the transition from acute to chronic lesions. The predominance of Th2 cytokines in the acute phase, such as IL-4 and IL-5, stimulates eosinophils, which produce IL-12, thereby activating Th1 cells and undifferentiated T cells to produce Th2 responses, causing a negative feedback to produce IFN-γ, and maintaining the AD lesion over an extended period (Figure 2).

The stratum corneum is the permeability barrier between the body and the external environment, and thus when it is impaired, increased transdermal water loss causes xerosis and intense pruritus. The barrier is compromised due to an overexpression of an enzyme that hydrolyzes sphingomyelin, producing free fatty acid and sphingosylphosphorylcholine, an inducer of keratinocyte proliferation and up-regulator of plasminogen activator, resulting in decreased ceramides. Additionally, scratching from pruritus induces trauma and further insult to an already compromised stratum corneum, which triggers keratinocytes to release proinflammatory cytokines. It is also because of this defective barrier that microorganisms such as S. aureus enter and colonize eczematous skin. Toxins released by microbes further interfere with ceramide metabolism, as cytolytic alpha toxin causes keratinocyte damage and superantigenic toxin causes release of TNF-alpha and Beta-hemolysin, which interfere with keratinocyte metabolism. These toxins also prevent keratinocytes from producing antimicrobial peptides to kill S. aureus.

Mechanism of Action for Phototherapy in AD: Many studies have demonstrated the beneficial effects of phototherapy in treating AD. The intradermal mRNA expression of IFN-γ, IL-12, and anti-IL-4 p55 protein was successfully downregulated during the course of UVA1 therapy, whereas IL-4 mRNA expression remained relatively unchanged even after those with chronic AD improved under treatment. The high efficacy of UVA1 phototherapy in the treatment of AD can be attributed to the combination of UV-light induced apoptosis of T lymphocytes as well as the reduction of Langerhans cells and mast cells in the dermis. Preventing Langerhans cells and mast cells from exiting the epidermis results in a decreased number of Ig-E binding cells in the dermis. Phototherapy induces the immunosuppressive mechanisms of the body, such as suppressing the antigen-presenting function of Langerhans cells, inducing apoptosis in infiltrating T cells, causing DNA damage, and halting the rapid accumulation of epidermal keratinocytes. Colonization by Staphylococcus aureus and Pityrosporum orbiculare is decreased through the use of UV radiation. UV light also increases the thickness of the stratum corneum and therefore results in smaller eczematous reactions due to a decreased penetration of antigens. Thus, UV light exerts...
its beneficial effects through a multitude of mechanisms. Although AD is the primary disease explained above, a similar mechanism of action for UV-based therapy can be applied to PN and LSC owing to their similar inflammatory nature.

**PRURIGO NODULARIS (PN)**

**Pathogenesis of PN:** A background of atopic diathesis has been suggested for PN after examining the history of AD, allergic rhinitis, and bronchial asthma.47,48 Tanaka et al. found examining the history of AD, allergic rhinitis, diathesis has been suggested for PN after Pathogenesis of PN:

A background of atopic PRURIGO NODULARIS (PN)

LSC owing to their similar inflammatory nature. explained above, a similar mechanism of action mechanisms. Although AD is the primary disease of PN.53 Dermal Langerhans cells are increased in PN, suggesting their involvement in the development or persistence of PN.37 In addition, the numbers of Merkel cells are increased in PN at the basal cell layer, explaining the abnormal sensitivity to touch from these slowly adapting sensory touch receptors.18

**Mechanism of Action for Phototherapy in PN:** UV light hinders rapid epidermal cell turnover and thereby leads to a reduction in pseudopitheliomatous hyperplasia of the epidermis.39 PN patients have an increase in the number of nerve fibers in the papillary dermis.60 These nerve fibers demonstrate immunoreactivity for SubP and CGRP and thus mediate the cutaneous neurogenic inflammation and pruritus in PN. It is postulated that MEL modulates the release of these neuropeptides.61-63 The long remission noted for MEL could be due to inhibition of neuropeptide releases, which cause pruritus and can consequently perpetuate the rubbing, scratching, and picking cycle. MEL treatment causes a depletion of T cells and decreases proliferation index of keratinocytes.64 PUVA downregulates CGRP and Th2 cytokines and depletes epidermal dendritic cells.65-67 The longer wavelengths used in PUVA penetrate the anacanthic thick epidermis more than classical NB-UVB.65-67 NB-UVB induces apoptosis of dermal mast cells and reduces the release of neuropeptides such as SubP by decreasing epidermal nerve fibers.56,57 Nitric oxide and IL-2 have also been implicated in the pathogenesis of uremic pruritus, both of which are decreased by NB-UVB.56-60 Schultz et al. suggest the response to UVB indicates a deposition of some substance in the skin that is degraded or inactivated by the light. Because uremic patients respond to cholestyramine, and phototherapy serves to clear bilirubin in jaundiced premature infants, bile salts were considered to be involved in UP pathogenesis.83 Individuals with advanced CRF had higher levels of serum total bile acids when compared to controls, and those with pruritus had higher levels of bile acids than those without pruritus. Thus, the intensity of pruritus correlated with bile acid concentration.82 Certain bile acids also cause cytotoxicity to mastocytes, thereby releasing histamine.83

UVB therapy is beneficial for patients with UP. Possible mechanisms include reduction in skin divalent-ion content, reduction in Vitamin A and retinol content, stabilization of or reduction in number of mast cells, detoxification of undetermined pruritogenic substances, photoactivation of antipruritogenic substances, and changes in the excitability of epidermal nerve endings. Mast-cell proliferation, degranulation, and subsequent histamine release plays a role in uremic pruritus (Figure 4). Histamine secretion is evoked by an increased release of SubP.59 NB-UVB induces apoptosis of dermal mast cells and reduces the release of neuropeptides such as SubP by decreasing epidermal nerve fibers.56,57

**UREMIC PRURITUS (UP)**

**Pathogenesis of UP and Mechanism of Action for Phototherapy in UP:** Although the pathogenesis of UP is not completely understood, it is known to present with dystrophic neurotrophic changes in cutaneous nociceptor nerve endings, with a "microinflammatory" state of increased Th1 markers, chemokines, and interleukin-6 (IL-6).73,74 It also causes calcium-phosphate imbalance, hyperparathyroidism, anemia, increased serum histamine levels, and peripheral neuropathy.73,74

UVB therapy is beneficial for patients with UP. Possible mechanisms include reduction in skin divalent-ion content, reduction in Vitamin A and retinol content, stabilization of or reduction in number of mast cells, detoxification of undetermined pruritogenic substances, photoactivation of antipruritogenic substances, and changes in the excitability of epidermal nerve endings. Mast-cell proliferation, degranulation, and subsequent histamine release plays a role in uremic pruritus (Figure 4). Histamine secretion is evoked by an increased release of SubP.59 NB-UVB induces apoptosis of dermal mast cells and reduces the release of neuropeptides such as SubP by decreasing epidermal nerve fibers.56,57 Nitric oxide and IL-2 have also been implicated in the pathogenesis of uremic pruritus, both of which are decreased by NB-UVB.56-60 Schultz et al. suggest the response to UVB indicates a deposition of some substance in the skin that is degraded or inactivated by the light. Because uremic patients respond to cholestyramine, and phototherapy serves to clear bilirubin in jaundiced premature infants, bile salts were considered to be involved in UP pathogenesis.83 Individuals with advanced CRF had higher levels of serum total bile acids when compared to controls, and those with pruritus had higher levels of bile acids than those without pruritus. Thus, the intensity of pruritus correlated with bile acid concentration.82 Certain bile acids also cause cytotoxicity to mastocytes, thereby releasing histamine.83
Table 1: Comparison of Mechanism of Action of Phototherapy in Pruritic Disorders

<table>
<thead>
<tr>
<th>Disease</th>
<th>Type of Phototherapy</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic Dermatitis</td>
<td>UVA1</td>
<td>↓IFN – gamma ↓T cells ↓Langerhans cells ↓Mast cells ↓IgE binding ↓colonyization by Staphylococcus aureus and Pityrosporum orbiculare ↓Stratum corneum thickness</td>
</tr>
<tr>
<td>Prurigo Nodularis</td>
<td>MEL</td>
<td>↓epidermal cell turnover ↓neuropeptide release ↓T cells</td>
</tr>
<tr>
<td>PUVA</td>
<td></td>
<td>↓CGRP ↓Th2 cytokines ↓Dendritic cells</td>
</tr>
<tr>
<td>Uremic Pruritus</td>
<td>UVB</td>
<td>↓Skin-divalent ions ↓Vitamin A and Retinols ↓Mast cells ↓SubP ↓Nitric oxide ↓IL-2 ↓Antipruritogenic substances</td>
</tr>
</tbody>
</table>

**Conclusion**

The mechanisms of action for phototherapy in each of the discussed pruritic disorders are unique and dependent on the pathophysiology of the disease. Phototherapy decreases pruritus in AD, PN, and UP through its apoptotic and anti-inflammatory actions and is therefore a useful therapeutic modality for these disorders. Due to the similarity in mechanisms of these diseases, there is sufficient evidence to support the use of various forms of UV-based treatment for reducing pruritus and its associated manifestations.

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The Cutaneous Manifestations of Metastatic Lung Cancer: Case Report and Review

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Abstract
Cutaneous metastasis comprises a tiny minority of skin tumors, estimated at 2%, and its timely diagnosis is extremely important to the clinical course of patients. Cutaneous metastasis of all primary systemic cancers usually indicates a poor prognosis with only a few months of survival time. Lung cancer remains the leading cause of cancer-related death among men and women in the United States. This article highlights an atypical presentation of lung metastasis to the skin and provides an overview of other uncommon and common cutaneous effects of lung cancer in general.

Introduction
Although uncommon in clinical practice, cutaneous metastasis is important to keep on a clinical provider’s list of differential diagnoses. Lung cancer continues to earn listings as the “most common cause of cancer-related deaths in both men and women,” “cancer most likely to metastasize in general,” and, affecting dermatologists particularly, “most common tumor to metastasize to the skin in males,” particularly in men over 40. The data reinforce the importance of having a low threshold for biopsy, especially if patient history directs.

Case Presentation
An 83-year-old male presented to our dermatology clinic with a complaint of a rash on his lower abdomen for approximately two months. The patient's rash was asymptomatic. He had cataract surgery planned, which was put on hold due to this rash, which he attributed to a reaction from EKG leads placed in the area of the rash upon his pre-op clearance studies. He was sent to the ER for a suspected cellulitis-type infection, and subsequently we were consulted. His past medical history was notable for intestinal resection for colon cancer resulting in the use of an ostomy bag for more than 18 years. He also had a history of lung cancer for which he underwent partial lobectomy of the right lower lobe along with radiation two years prior for a T2aN0M0 lung tumor non-small-cell type (adenocarcinoma). He had regular follow-ups with all of his subspecialists and primary care providers, and review of systems was negative.

On exam, his left lower abdomen was significant for an intact ostomy bag, with superior and bilateral lower abdominal quadrants demonstrating large, indurated, erythematous and violaceous blanchable plaques oriented horizontally, not extending below his pannus fold.

The left aspect of the rash had a “peau d’orange,” palpable nodularity (Figure 1).

Two 4.0 mm punch biopsies were performed at initial consultation, with an initial differential diagnosis inclusive of infection; panniculitis; erysipeloid and/or carcinoma en cuirasse-like presentation of underlying carcinoma; atypical angiosarcoma, due to patient history of radiation to the area; and interstitial granulomatous dermatitis.
Pathology revealed findings consistent with metastatic carcinoma, lymphangitic-type spread (Figure 2, H&E). The immunostain pattern of CK-7 positive (Figure 3), TTF-1 positive (Figure 4), and CK-20 negative (Figure 5) favored primary lung carcinoma.

The patient was then referred to hematology/oncology. On close review of past records and considering findings on new imaging demonstrating two new masses at an area adjacent to his previous partial lobectomy, this was thought to be a recurrence of a previous diagnosis of non-small-cell cancer. He was quickly started on a chemotherapy regimen of gemcitabine and followed regularly in dermatology clinic to track his metastatic lesions. Although initially given an ominous prognosis, the patient is doing very well. His abdominal lesions are fading, which correlate to his overall response to treatment (Figure 6, almost one year after initial biopsy).

Discussion

Although usually detected in a patient with known and widespread disease, on occasion cutaneous metastasis may be the presenting sign of clinically silent lung cancer. Early detection of cutaneous metastasis, then, affects how fast a patient may be diagnosed and placed on appropriate therapy by hematology/oncology. Further, depending on the morphologic presentation, cutaneous metastasis may not only help with diagnosis of otherwise asymptomatic disease, as with the case presented in this article, but may also serve as a marker in monitoring response to chemotherapy.

Reviewing statistics involving cancers most likely to metastasize to the skin may be confusing. The percentage of patients with metastatic disease with cutaneous involvement depends upon the particular malignancy. When looking at the proportion of all patients with metastatic disease who have developed metastasis particularly to the skin, melanoma dominates. Differences also occur when factoring in age and sex of patients.

When approached broadly, one retrospective study of 4,020 patients showed that breast, melanoma, and lung, in that order, top the list for most common cancers to spread to the skin. For older men who present with skin metastases, lung cancer is the most common primary, at about 24%, followed by colorectal cancer, melanoma, and carcinoma of the oral cavity. In women, lung cancer ranks fourth after primary breast cancer, colon cancer, and melanoma. Overall, if a patient has lung cancer, their chance of cutaneous metastasis varies, ranging 1% to 12%. Although the skin is not the first organ it usually spreads to, when it does it does so quickly, with a mean time of less than six months.

Clinical Presentation

In most cases, skin metastases present after the diagnosis of a known primary. Occasionally, these lesions may be the inciting event that eventually leads to diagnosis of underlying disease. In one study, 11 out of 21 patients with metastatic lung cancer had their metastatic skin lesions present as the first sign of extranodal disease.

Skin metastasis from lung cancer does not have a typical presentation. Anatomically, the chest, abdomen, and head and neck are common sites. Morphologically, lesions are usually nodular, painless, and may be either single or multiple. The scalp, head and neck are the most common sites, along with anterior chest and abdomen. Several atypical presentations of metastatic lung cancer have been described including spread to both upper and lower limbs, gingiva, genitalia, and incision sites. Although nodules are the most common presentation, different patterns have been reported including zosteriform, ulcerative, fungating, and erysipeloid-like presentations.

Diagnosis

Diagnosis is made on biopsy. Patterns on H&E are generally either nodules of tumor cells within the dermis or cords of atypical tumor cells mixed within a fibrotic stroma.

The most common type of lung cancers reported to metastasize to the skin are adenocarcinoma and large-cell carcinoma, followed by squamous-cell. A couple of studies from Japan have demonstrated that large-cell carcinoma has the highest incidence of metastasis to the skin.

On histology, metastatic adenocarcinoma of the lung may display glandular, well-differentiated structures with mucin, in which case GI, ovarian, breast and kidney metastases must be ruled out. CK 20 paranuclear dot positivity helps differentiate from Merkel-cell carcinoma. Other types of lung cancer that rarely metastasize to the skin include mesothelioma and bronchial carcinoid, which usually show more of a trabecular pattern and sometimes present with carcinoid syndrome.

Immunohistochemistry (IHC) has evolved into a reliable tool in diagnosis. An IHC battery of an unknown cutaneous metastasis helps narrow down the differential diagnosis. Although not originally studied in the skin, useful markers include CK 7 and CK 20 and anti-thyroid transcription factor (TTF). CK 7 is very sensitive and is positive in virtually all cases of primary lung adenocarcinoma; however, it has lower specificity since it is also positive in many other types of lung carcinoma (70% of large-cell neuroendocrine, 40% of large-cell, and 23% of squamous-cell). Anti-TTF is a sensitive and specific marker that identifies pulmonary origin of an adenocarcinoma, bronchoalveolar carcinoma, and small-cell carcinoma if a thyroid origin is excluded.

Overall, IHC panels are not substitutes for the big-picture approach to diagnosis, incorporating a thorough review of systems and history, exam, and screening tools such as appropriate bloodwork and radiologic studies. Communication of the above to pathology and consulting specialists may prove to be invaluable.

Treatment and Prognosis

Treatment approach for any cutaneous metastasis is multidisciplinary. If the cutaneous metastases are localized and discrete, surgery alone or combined with chemotherapy and/or radiation may be possible for functional or even cosmetic reasons. Some studies have shown that treatment of localized disease with surgery or combination modalities may increase survival. If disease is more disseminated, chemotherapy remains the best option. Sometimes during chemotherapy, cutaneous lesions may be thought of as a marker for response to therapy. Patients without cutaneous metastasis tend to live longer than those who present with them. Mean survival is short, usually five to six months after diagnosis of cutaneous metastasis. Living past a year, as with our patient, is unusual but has been reported.

Conclusion

Although uncommon, cutaneous metastasis may occasionally be the presenting sign of an internal
malignancy. Since lung cancer is so prevalent, it is an important differential diagnosis of any unexplained, fresh lesion in someone with risk factors. These lesions are usually on the trunk, head and neck, but could present practically anywhere and with many morphologies, like the erysipeloid and peau d’orange presentation in this case. Despite an ominous prognosis, early recognition and timely diagnosis usually confers a better survival time, as with our patient. Biopsy is essential, with immunohistochemical panels proving to be helpful and guiding tools. Likely these panels will become more sophisticated and expand their utility in terms of determining prognosis and targets for therapy.

References

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Loose anagen syndrome is a rare condition of abnormal hair cornification leading to excessive and painless loss of anagen hairs from the scalp. The condition most commonly affects young females with blonde hair, but males and those with darker hair colors can be affected. Patients are known to have short, sparse hair that does not need cutting, and hairs are easily and painlessly plucked from the scalp. No known treatment exists for this rare disorder, but many patients improve with age.

Case Report
We present the case of a 27-month-old female presenting to the clinic with a chief complaint of diffuse hair loss for the last five months. The mother stated that she began finding large clumps of hair throughout the house, most notably in the child's play area. She stated that the condition had progressed to where she is afraid to wash or comb her hair and is exceptionally careful changing her clothes, as even minor pulling on the hair will result in additional loss. The mother reports that her once long, curly locks are now short and straight, and no hair will grow past her neck line. The patient had no notable medical history and took no daily medicines. An older brother and sister had no similar findings. She was growing well and meeting all developmental milestones. The mother denied any major traumas, psychologically stressful periods or any major illnesses that the patient or the family experienced in the last year. The mother denied any hair manipulation or hair-pulling behaviors and stated that the daughter is so concerned about her hair being pulled out she is now refusing to play in close proximity to her siblings or friends.

On physical examination, we found a shy white female with sparse blond hair. Her hair reached only to the neck, and the mother stated that she does not need haircuts (Figures 1 and 2). She appeared generally healthy and eventually began playing in the examination room. She had no other skin, dental or nail findings. Her eyebrows, body hair and eye lashes were unaffected.

Laboratory evaluation done by her pediatrician, including complete blood count, renal panels, liver panel, anti-nuclear antibody and thyroid studies, were all within normal limits.

A hair-pull test was done, with more than 10 hairs being pulled without pain. The mom and patient were very upset when this test was done, as it was not fully explained, and refused further hair pulls. They did allow me to pull lightly on individual hairs, which repeatedly were easily pulled from the child's head without pain. A trichogram was done, which showed a distorted anagen bulb with a “rumpled sock” appearance (Figure 3).

Based on the history and physical examination, a diagnosis of loose anagen syndrome (LAS) was made. The mother and child were advised on the natural history of this condition and were offered a trial of minoxidil 5% hair solution to be applied to her scalp daily. We encouraged her to continue being mindful of and avoid activities that would result in further hair loss such as combing, shampooing and pulling narrow-necked clothing over her head. The patient will continue to follow with us, and although not happy with her condition, they were relieved to have received a diagnosis.

Discussion
Loose anagen syndrome is an uncommon condition characterized by loosely attached hairs of the scalp leading to diffuse thinning with poor growth, thus requiring few haircuts. It was first described in 1984 by Zaun, who called it “syndrome of loosely attached hair in childhood.” A few years later, Price and Gummer along with Hamm and Traupe began describing similar cases in the American literature and coined the current term “loose anagen hair syndrome,” or LAHS. The annual incidence has been estimated at 2.5 cases per million, with 6.37 cases in boys as compared to girls. However, it has been suggested that the condition may be underestimated in boys due to differences in hairstyle. Cases described within families occurring in an autosomal-dominant pattern further suggest a ratio that is probably closer to 1.6-8

The classical clinical picture is that of a young girl with blonde hair that can be easily and painlessly plucked. Even so, cases do occur frequently in boys and adults, as well as in individuals with dark hair. Recent formal reports document cases from Egypt and India. Three phenotypes, types A, B, and C, have been described. In Type A, hair is sparse and does not grow long. In Type B, the individual has unruly hair that is either diffuse or patchy. In Type C, the hair appears normal but has excessive shedding and loose anagen hairs. The eyebrows and eyelashes are not affected.

A diagnosis relies on the presence of loose anagen hairs, and the need to rule out other causes of diffuse hair loss, such as trichotillomania or alopecia areata.
hairs that when examined under the microscope display derangements involving the inner and possibly the outer root sheaths. A hair-pull test or trichogram can be performed in order to support the diagnosis, although there are several drawbacks. Few controlled studies have been done in order to properly define the parameters for a positive test. Authors have suggested using greater than 10 loose anagen hairs, compared to the usual one or two hairs in normal subjects, as the cutoff for constituting a positive pull test. On trichogram, greater than 70% loose anagen hairs compared to the normal 10% is considered positive. To avoid overdiagnosis, one must keep in mind that anagen hairs can be found on normal scalp; their presence is neither pathognomonic nor specific. The differential for LAS should include alopecia areata, tinea capitis, trichotillomania, traction alopecia, and secondary syphilis. See Table 1 for differential.

Much research has been done, although the precise pathogenesis of this syndrome has yet to be elucidated. The reigning theory is that of inner-root-sheath derangement leading to poor adhesion between the cuticle of the inner root sheath and that of the hair shaft, causing poor anchoring. Normal anagen hair is a complex structure requiring orderly development and maturation in order to achieve the proper hair follicle. Deranged anagen follicles of LAS exhibit characteristic features under both light and electron microscopy. The keratinized cell layer exhibits premature keratinization with dyskeratosis and thus poor anchoring of the hair shaft to the scalp. It is hypothesized that this mutation may lead to instability of the intermediate filament network and thus poor anchoring of the hair shaft to the scalp. It was not until recently that keratins of the inner root sheath, K12,28-29 were described. Molecular analysis for possible mutation in these genes has yet to be done.

Although the majority of cases have been sporadic, as previously mentioned, there is some evidence of autosomal-dominant inheritance with variable penetrance. There have been associations with certain conditions such as Noonan’s syndrome, coloboma, hypohidrotic ectodermal dysplasia, and woolly hair. There is no agreed upon or universally effective treatment for LAS. In some individuals, the condition improves with age, most notably around puberty. However, in some individuals the condition persists into adulthood. A recent case report showed good results using daily therapy with minoxidil without any side effects in a 2-year-old patient. While minoxidil is generally safe and inexpensive, there are some considerations when prescribing to pediatric patients. Rare cases of reversible generalized hypertrichosis have been reported in children using excessive amounts of minoxidil for alopecia areata, so caution should be used. Another consideration in pediatric patients is excessive systemic absorption, which could potentially cause cardiovascular symptoms such as tachycardia, palpitations and dizziness, so patients and their caregivers should be advised to monitor for side effects.

Loose anagen syndrome is an uncommon condition that can cause a significant psychosocial impact in patients and families. More research is needed to fully understand the cause of this condition and to improve the limited treatment options available. Patients should be advised that this condition is thought to be benign in nature, and many patients’ hair normalizes with age. We have chosen to recommend minoxidil to our patient while warning the mother of the potential of cardiovascular side effects and hypertrichosis. We will continue to follow her progress.

**References**


**Table 1. Differential Diagnosis of Pediatric Alopecia**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Findings</th>
<th>Pathology</th>
<th>Hair-pull Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loose Anagen Syndrome</td>
<td>Diffusely thin hair that tends to not grow beyond the shoulders. Bald patches may be present. Hair may be dull, unruly, or matted.</td>
<td>“Rumpled sock” look to anagen bulb on trichogram.</td>
<td>&gt;10 hairs painlessly pulled. Individual hairs easily pulled.</td>
</tr>
<tr>
<td>Lupus</td>
<td>Erythematous papules and plaques with scale. Lesions expand centrifugally. Follicular plugging with atrophy, scarring, and telangiectasia. Dark-skinned individuals may have peripheral hyperpigmentation with central hypopigmentation.</td>
<td>Follicular red dots on trichoscopy. On histology, vascular interface change with chronic inflammation of eccrine sweat glands and arrector pil. Increased dermal mucin. IgG and C3 deposition at D-E junction.</td>
<td>Normal</td>
</tr>
<tr>
<td>Alopecia Areata</td>
<td>Non-scarring, round-to-oval patch of hair loss. Totalis, universalis, ophiasis, and reticular variants. Nail changes may be present. May be chronic and relapsing.</td>
<td>Yellow dots, exclamation mark appearance, and dystrophic hairs on trichoscopy.</td>
<td>May be positive in the diffuse variant.</td>
</tr>
<tr>
<td>Trichotillomania</td>
<td>Patchy or full alopecia of hair-bearing areas, most commonly the scalp. Patches have bizarre and irregularly shaped borders with hairs of varying lengths. Occiput sparing.</td>
<td>On histology, incomplete, disrupted follicular anatomy, trichomalacia, pigment casts.</td>
<td>Normal</td>
</tr>
<tr>
<td>Tinea Capitis</td>
<td>Most commonly presents as alopecia with or without scale. Presentation can range from a non-inflammatory scaling resembling seborrheic dermatitis to severe pustulosis also known as a kerion.</td>
<td>Comma hair on trichoscopy. Infection with T. tonsurans (&gt;90% of cases in the U.S.) results in the classic black dot appearance.</td>
<td>Normal</td>
</tr>
<tr>
<td>Telogen Effluvium</td>
<td>Thinning involving the entire scalp and other hair-bearing regions.</td>
<td>Mixture of normal anagen and telogen hairs with &gt;20% telogen hairs.</td>
<td>Positive for two or more normal telogen hairs.</td>
</tr>
</tbody>
</table>


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Anetoderma Secondary to Mid-dermal Elastolysis

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Abstract
Anetoderma usually presents as circumscribed, 1 cm to 2 cm patches and plaques of flaccid skin secondary to loss of dermal elastic tissue. Lesions often occur in the neck, upper extremities, chest, and back. On histopathology, one sees complete loss of dermal elastin involving the papillary and reticular dermis, with infiltration of plasma cells and histiocytes. A 40-year-old female with no significant medical history presented with multiple round, 1 cm to 2 cm lesions scattered on her upper back and chest. Skin biopsy demonstrated elastic-fiber loss localized to the mid-dermis along with a lymphohistiocytic infiltrate with elastophagocytosis and active inflammatory phase in the papillary and mid-reticular dermis. The histopathological findings were consistent with mid-dermal elastolysis with advancing inflammation, and the clinical features were consistent with anetoderma. The microscopic examination revealed an active inflammatory phase of mid-dermal elastolysis, supporting the postulated theory that MDE may be part of a continuous spectrum with anetoderma.

Case Report
A 40-year-old female with no significant medical history presented with multiple round, 1 cm to 2 cm lesions scattered throughout the upper back and chest. The lesions were characterized by lax, wrinkled skin with underlying palpable depression (Figure 1). They were often preceded by two to six months of local erythema and had increased in number over the past two years. No response was seen after topical steroids. Skin biopsy and elastic-fiber staining demonstrated elastic-fiber loss in the mid-dermis along with a lymphohistiocytic infiltrate with evidence of elastic-fiber phagocytosis and an active inflammatory background in the papillary and reticular dermis (Figures 2, 3 and 4). This is a case demonstrating the development of anetoderma as seen by the progressive inflammation and elastophagocytosis in the papillary and reticular dermis that developed in the setting of mid-dermal elastolysis (MDE).

Discussion
Mid-dermal elastolysis (MDE) is a rare acquired disorder of elastic-tissue degradation limited to the mid-dermis. It consists of a clear band of mid-dermal elastic-tissue loss as a result of inflammatory destruction of dermal elastic fibers. The elastic-tissue loss occurs as a result of inflammatory destruction of dermal elastic fibers. Remnants of abnormal elastic tissue and granuloma formation may be present, along with evidence of elastophagocytosis. Elastic tissue is usually preserved around hair follicles, resulting in perifollicular papules on the affected skin.
The condition was first described in 1977 by Shelley and Wood, and since then, there have been approximately 80 cases reported in the literature. It has a female predominance and presents clinically as diffuse, fine wrinkling on the neck, arms, and trunk in patients between the ages of 30 and 50 years. It is classified into three types: type I, or classic type, with well-demarcated patches with wrinkling; type II, with perifollicular papular protrusions; and type III, with reticular/annular patches with wrinkling.

Mid-dermal elastolysis has been reported to originate from involuting sites of granuloma annulare that started as a patchy, slightly indurated and violaceous eruption involving the neck and trunk and eventually became atrophic, pale and wrinkled. Urticaria, atopic dermatitis, Sweet's syndrome, phototoxic dermatitis, and pityriasis rosea have also been described to precede MDE. Anetoderma can also occur in areas of preceding erythema, which is consistent with our patient's clinical presentation.5

Anetoderma, also known as dermatitis maculosa atrophicans, is an elastic-tissue disorder that shows focal loss of elastic fibers in the dermis. The term "anetoderma" is derived from the Greek words "anetos," meaning slack, and "derma," meaning skin. Sac-like tumors that herniate upon palpation were first described by Schweninger and Buzzi in 1891, but anetoderma was first officially described in 1892 by Jadassohn. It usually presents as multiple, circumscribed, 5 mm to 25 mm areas of flaccid skin with fine wrinkling that can occur in the neck, upper extremities, chest, and back. The lesions are skin color but can present with a blue-white discoloration. Affected areas of skin can herniate after palpation ("buttonhole" sign) and can show central depressions.

Anetoderma is classified as either primary (idiopathic) or secondary. Primary anetoderma is divided in two types: Jadassohn-Pellizzi type, which has preceding inflammatory lesions, and Schweninger-Buzzi type, which has no preceding inflammation. It is seen more commonly in women than men and occurs in individuals between 15 and 25 years of age. Secondary anetoderma may be associated with tumors, depositions, autoimmune disorders, infections, drugs and inflammatory cutaneous disorders. The loss of elastic tissue is usually localized to those sites of previous skin lesions caused by the primary disease.

On histopathology, there is focal loss of elastic fibers in the dermis with infiltration of plasma cells and histiocytes. The elastic fibers can have an irregular shape and may be fragmented or engulfed by macrophages. Remnants of abnormal elastic tissue and granuloma formation may be present.

Activated macrophages and fibroblasts from existing inflammatory processes can destroy dermal stromal elements by releasing proteolytic enzymes. UV light exposure and autoimmunity against elastic fibers are thought to contribute to the condition. Defects in the synthesis of elastin and dysregulation of elastic-fiber digestion by metalloproteinases (MMPs) also seem to play a role. Giant cells and elastophagocytosis may be present in both mid-dermal elastolysis and anetoderma. Emer et al. described a case of anetoderma that was instigated by penicillin G to treat syphilis in an HIV-positive patient without any previous skin complaints.

Mid-dermal elastolysis and anetoderma, both disease entities resulting from elastic-fiber degradation, are differentiated histopathologically by the extent and location of elastic-fiber loss. The former consists of elastic-tissue loss localized to the mid-dermis, and the latter is characterized by elastic-fiber loss in the entire dermis.

It has been speculated that MDE and anetoderma are within the same spectrum of disorders, as they present similar histopathological configurations to different extents, suggesting MDE may evolve into anetoderma secondary to long-standing inflammation. Our patient demonstrated a classic histopathology of MDE with secondary anetoderma resulting from an active inflammation and elastaphagocytosis, lymphocytes, plasma cells and histiocytes extending to the papillary and reticular dermis.

Mid-dermal elastolysis and anetoderma need to be differentiated from other connective-tissue diseases affecting elastic fibers, including cutis laxa, pseudoxanthoma elasticum (PXE), and PXE-like papillary dermal elastolysis. Post-traumatic scars, perifollicular elastolysis, papular elastolysis, pseudoxanthoma elasticum, focal dermal hypoplasia (Goltz syndrome), and nevus lipomatosus are other entities that may be included in the differential diagnosis of anetoderma.

Cutis laxa is an entity with redundant and loose skin seen on the eyelids, cheeks, shoulder girdle, abdomen and neck. It presents clinically with premature aging secondary to loose skin folds with or without internal organ involvement. In this condition, the whole dermis is affected with diminished and fragmented elastic fibers, and it can occur in an acquired or hereditary form.

Pseudoxanthoma elasticum (PXE) and PXE-like papillary dermal elastolysis present as cobblestoning yellow papules and redundant folds in flexor areas. The former can be associated with ocular and cardiovascular involvement. It occurs in sites of previous scars, axilla, groin, and lateral neck and consists of clumped and calcified elastic fibers in the mid-dermis. The latter is seen in inflammatory folds, lower abdomen, axilla, and neck, and has a band-like pattern of clumping and fragmentation of elastic tissue in the papillary dermis.

Intralesional triamcinolone injections and systemic administrations of diprosone, aspirin, penicillin G, vitamin E, and inositol nicotinate have been used to treat existing anetoderma lesions without success. Administration of hydroxychloroquine, colchicine, and aminopropic acid, as well as surgical excision, have resulted in some improvement. Cho et al. reported anetoderma presenting after Stevens-Johnson syndrome successfully treated with ablative carbon dioxide fractional laser. Lasers destroy the hydrogen bonds in the collagen triple helix, instigating an inflammatory cascade that is believed to be responsible for rebuilding stable and more native-like collagen and elastic fibers, thereby reverting the pathological process.

Conclusion
We report a case demonstrating the development of anetoderma as seen by progressive inflammation and elastaphagocytosis in the papillary and reticular dermis that developed in the setting of mid-dermal elastolysis (MDE). The histopathological findings were consistent with mid-dermal elastolysis with active inflammation, and the clinical features were consistent with anetoderma. The histologic examination revealed elastic fiber loss localized to the mid-dermis along with a lymphohistiocytic infiltrate with elastaphagocytosis and active inflammatory phase in the papillary and mid-reticular dermis. Such areas of active inflammation indicate the development of anetoderma in the pre-existing MDE background as elastic-fiber degradation spread beyond the mid-dermis to involve the papillary and reticular dermis.

Anetoderma often occurs from existing inflammatory processes that lead to elastic-fiber destruction, thus the overall findings in this case may support the theory that MDE is part of a continuous spectrum with anetoderma.

References

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Generalized Linear Porokeratosis: A Case Report and Discussion

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Abstract
Linear porokeratosis is a clinical variant of porokeratosis that usually arises in infancy or childhood, but may present in adulthood. There are two presentations, the first being more common and localized. It is unilateral and confined to one extremity. In the rarer version, the lesions affect multiple extremities and the trunk, appearing in a zosteriform pattern. Of all the variants of porokeratosis, linear porokeratosis has the greatest chance of malignant transformation, with squamous cell carcinoma and basal cell carcinoma being the most common. We present a case of a 57-year-old man with reddish-brown skin lesions showing central atrophy with surrounding scale, hyperpigmentation and erythema present on the right posterior back, right arm, right lateral leg and right buttock. Within the lesion on his leg there was noted actinic damage. There are numerous treatment options for porokeratosis, with varying benefits and risks. It is important to take into consideration the age of the patient and the morphology of the lesions being treated in order to leave the patient with the most cosmetically pleasing outcome. For our patient, we elected to treat with topical imiquimod 5% and fluorouracil 5% because of the large areas of involvement.

Introduction
The porokeratoses are a group of acquired or genetic disorders of epidermal keratinization characterized by singular or multiple, annular, atrophic lesions surrounded by a keratotic border. The peripheral keratinization of the demarcated lesions corresponds to a typical histopathologic feature, namely, the cornoid lamella. Various forms of porokeratosis have been established based on the clinical course of the disease, the morphology and the distribution of the lesions. Linear porokeratosis is a clinical variant of porokeratosis. It consists of one or more plaques that are similar in appearance to classic porokeratosis; however, the plaques follow the lines of Blaschko and are most commonly on the extremities. When linear porokeratotic lesions have a typical clinical appearance, it is easy to diagnose. However, in lesions that are smaller and have less elevation of borders, it may be confused with other linearly arranged lesions. Differential diagnosis includes inflammatory linear verrucous epidermal nevus, linear lichen planus, incontinentia pigmenti (stage II), linear psoriasis, linear Darier’s disease, and lichen striatus. We present a case of linear porokeratosis with arising SCC in situ in a 57-year-old male.

Case Report
A 57-year-old Caucasian male presented for evaluation of a lesion on the left lateral arm and was found to have extensive skin lesions showing central atrophy with surrounding scale, hyperpigmentation and erythema. The lesions were confined to the right side of his body and followed the lines of Blaschko. They were present on the right posterior back in a curved/whorled fashion, the right arm, and the right lateral leg and buttock (Figures 1-4). Extending down the lateral leg, it was evident that the inferior portion had actinic activity present (Figure 5). A shave biopsy was taken during his first visit, showing SCC in situ. Two punch biopsies taken

![Figure 1](image1)
![Figure 2](image2)
![Figure 3](image3)
![Figure 4](image4)
of the lower extremity showed definitive cornoid lamellae with thin and flattened epidermis. Subtle interface change with few necrotic keratinocytes was also noted. There was mild superficial perivascular lymphocytic inflammation with melanophages. Focal parakeratosis with few superficial epidermal dyskeratotic keratinocytes was noted. (Figure 6) Past medical history, medications, allergies, social history, and family history were noncontributory.

The patient reported that he developed the lesions in 1967 when he was 12 years old. At this time he suffered from an episode of severe sun exposure with peeling and blistering on his chest, arms and back. Shortly after, he noticed the development of vesicles that started on his right arm, no bigger than the size of a pustule. The vesicles then spread to his right leg and back. He reported that his lower extremities were not exposed and did not get sunburned. After a few years, he presented to his primary care physician, who referred him to a skin specialist who thought the lesions were due to “shooting up” drugs. No biopsy was performed at that visit.

At 18 years of age, the patient entered the Navy. The lesions had remained constant since appearing years before. He noticed that they would bleed and become erythematous during hot weather. Due to these symptoms, in approximately 1976 he saw a dermatologist in Hawaii at an Army hospital. A biopsy was taken; however, the diagnosis was never relayed to him and no further treatment was performed. Again during the 1980s, he visited a dermatologist with the Navy in Hawaii. He had a second biopsy performed and remembers being treated with a 5% “fading” cream that was applied to his right arm only and wrapped with cellophane. In approximately 2005, he was evaluated at an Air Force Base, where he saw a dermatologist. A biopsy was performed. He was told that it was not cancerous, and no further action was taken.

Pathogenesis
Porokeratosis is a premalignant disease of epidermal keratinization characterized by atrophic macules and patches with a surrounding border of hyperkeratinization. The cornoid lamella is the hyperkeratotic border of vertical mounds of parakeratotic corneocytes that lies in the periphery around the lesions. Clonal proliferation of atypical keratinocytes from the stratum corneum and superior epidermis, demonstrating abnormal terminal keratinocyte differentiation, leads to the formation of the cornoid lamella. The pathway that leads to the clonal proliferation of abnormal keratinocytes is not known; it has been thought that genetic susceptibility, UV-radiation exposure, viral infection, and immune status may be contributing factors. Immunodeficiency may be due to organ transplant, chemotherapy, chronic kidney disease, HIV, hepatitis C, or repeated trauma as well as other pathological processes. Mosaicism is a proposed genetic mechanism for two types of porokeratosis, porokeratosis of Mibelli and linear porokeratosis. Mosaicism occurs when cells within an individual have different genetic makeup. There is conflicting evidence as to the association between ultraviolet radiation and porokeratosis. Support for the relationship is due to the observation that disseminated superficial actinic porokeratosis (DSAP) occurs in individuals with extensive sun exposure, occurs on areas of sun-exposed skin, and occurs in experimental settings with the use of artificial ultraviolet radiation. However, the relative sparing of the face weakens the relationship between UV radiation and the development of porokeratosis. Also, treatment of DSAP with psoralen plus ultraviolet A (PUVA) has shown to improve lesions. Immunosuppression or immunodeficiency has been shown to increase the risk of porokeratosis. The evidence is due to reports of remission of porokeratosis after cessation of immunosuppressive therapy. Also, porokeratosis has developed in areas of long-term topical corticosteroid use.

Treatment
There are numerous modalities used for the treatment of porokeratosis. In general, treatment of linear porokeratosis is disappointing and contradictory. Treatment modalities include topical creams such as fluorouracil 5%, corticosteroids, retinoids, keratolytics, and calcipotriol; surgical treatments such as curettage, excision, cryotherapy, and electrodessication; laser treatment with carbon dioxide laser; and dermabrasion. Systemic retinoids can also be utilized as a method of clearance and prophylaxis.

For our patient, fluorouracil 5% and imiquimod 5% were selected as treatment options due to the large areas of the lesions and extensive actinic damage within each lesion. Fluorouracil 5% is a topical antineoplastic, anti-metabolite cream containing pyrimidine fluorouracil, used in the treatment of actinic keratosis and superficial basal cell carcinoma. It works by inhibiting DNA and RNA synthesis. Anti-metabolites block the replication of DNA by preventing the building blocks of DNA (the purines and pyrimidines) from being incorporated into DNA, which halts normal development and division. Imiquimod is an immune-response modifier that acts as a toll-like receptor 7 agonist. Like fluorouracil 5%, it is used to treat actinic keratoses and superficial basal cell carcinoma. Field therapy with imiquimod 5% is a treatment of choice on areas where surgery or other treatments may be complicated, difficult or otherwise undesirable. This is why it was selected for our patient, who had very large areas of skin involvement that would not have been surgically operable without skin grafts or other measures. Imiquimod’s mechanism of action is via stimulation of innate and acquired immune responses, leading to inflammatory-cell infiltration within the field of drug application followed by apoptosis of diseased tissue. Our patient, after being treated with fluorouracil 5% and imiquimod 5%, was clear of actinic keratosis within the plaques. He did not follow up, so definitive clearance is unable to be determined.

Biopsy
Biopsy of porokeratosis shows stacked, tightly packed parakeratotic cells that are well-differentiated from the rest of the corneocytes. The stratum granulosum is either absent or decreased, and the stratum spinosum may possess vacuolated or dyskeratotic cells. The defective desquamation of the corneocytes may be due to a decrease in the keratohyalin granules and lamellar bodies underneath the cornoid lamella. Biopsy of the underlying dermis shows mild perivascular mononuclear cell infiltrate. Fibroblasts also taken from the underlying dermis of a lesion have shown instability of the short arm of chromosome 3. The nuclei of keratinocytes beneath the cornoid lamella in the epidermal basal layer have shown over-expression of p53. It has been noted that this may explain the malignant potential of porokeratosis.

Discussion
Since its first description by Mibelli and Respighi in 1893, many new variants of porokeratosis have been described. A patient may develop more than one type of porokeratosis simultaneously or consecutively. Each variant consists of its own properties regarding morphology, distribution and clinical course. The initial lesions present in a centrifugal manner as keratotic papules. These lesions then progress, showing central...
atrophy with a collar of keratin. A biopsy of the lesion’s border shows parakeratotic cells stacked tightly, sticking out from the rest of the stratum corneum. This cornoid lamella is the hallmark of porokeratosis. Further manifestations include thinning of the stratum granulosum, dyskeratotic cells in the stratum spinosum and subsequent thinning of the epithelium. Abnormalities in the maturation of keratinocyte clones has been implicated in the pathogenesis of porokeratosis.

The most common forms of porokeratosis are:

- Classic porokeratosis of Mibelli (PM)
- Disseminated superficial acinic porokeratosis (DSAP) and its non-acinic variant, disseminated superficial porokeratosis (DSP)
- Linear porokeratosis
- Porokeratosis palmaris et plantaris disseminata (PPPD)
- Punctate porokeratosis, which might represent a variant of PPPD

Besides these, there are a few rare, atypical morphological forms such as facial porokeratosis, giant porokeratosis, punched-out porokeratosis, hypertrophic verrucous porokeratosis and reticulate porokeratosis.5 Porokeratosis ptychotropica is a recently described subtype of inflammatory perianal disease showing symmetrically distributed, reddish-brown papules and plaques involving the gluteal cleft and genital areas.13-15 Porokeratoma, otherwise known as porokeratotic acanthoma, is a tumor-like acanthoma showing cornoid lamellation characteristic of porokeratosis.6 These lesions have a keratotic or verrucous appearance and are commonly found on the limbs. Histologically, they have multiple and confluent cornoid lamellae. A rare congenital disorder of keratinization characterized by eccrine and hair-follicle involvement is known as porokeratotic adnexal ostial nevus (POAN). This name was proposed to incorporate porokeratotic eccrine ostial and dural duct nevus (PEODDN) and porokeratotic eccrine and hair-follicle nevus (PEHFN).17 Pruritic popular porokeratosis is a variant described in only about 10 previous reports in the English literature.18,19 This form of porokeratosis represents lesions that arise fairly abruptly in a patient with or without preexisting disseminated superficial porokeratosis and tend to resolve over months.19

Less-commonly reported clinical entities that share the histopathologic characteristic of cornoid lamellation include viral warts, some ichthyoses, naevoid hyperkeratosis, seborrheic keratosis, squamous cell carcinoma, basal cell carcinoma, verruca vulgaris, scars, milia, and solar keratosis.3 A differential diagnosis includes psoriasis, actinic keratoses, Darier’s disease, and lichen striatus, along with others.

Malignant transformation occurs in all of the five major forms of porokeratosis, with variable rates of transformation depending on the clinical variant. Lesions of linear porokeratosis have an increased risk of malignant transformation into squamous cell carcinoma, including Bowen’s disease, and basal cell carcinoma.20 A few risk factors have been established, including excessive sun exposure, radiation therapy, internal malignancies, and a family history of porokeratosis.2 It has been hypothesized that the increased malignant potential for linear porokeratosis may be due to allelic loss in addition to overexpression of the tumor suppressor gene p53 within linear porokeratosis lesions.21 Monitoring for suspicious lesions is key in the care of patients with porokeratosis.

**Conclusion**

Linear porokeratosis is a rare variant of porokeratosis that has an increased risk of malignant transformation. Individuals with this type should have regular follow-up visits and yearly skin exams. There are multiple treatment options, and each patient case is different.

**References**


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Permanent Imiquimod-induced Depigmentation

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Abstract

Imiquimod may be used as a topical therapy for actinic keratosis.1 We report on a patient treated with imiquimod for actinic keratoses who developed an inflammatory reaction, which subsequently resulted in depigmentation of the skin at the sites of imiquimod application. At nine-year follow-up, the patient still had skin depigmentation. We hope to increase awareness amongst dermatologists of this rare but potentially permanent adverse effect of imiquimod and discuss the possible mechanisms by which depigmentation may occur.

Introduction

Imiquimod is a topical immune-response modifier commonly used in dermatology. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of condyloma acuminata; non‐hyperkeratotic, non‐hypertrophic actinic keratosis; and superficial basal-cell carcinomas less than 2 cm in diameter located on the trunk (excluding anogenital area), neck, or extremities (excluding hands and feet).1

The most frequently reported dermatologic adverse reactions include localized erythema, xeroderma, and crusted skin.1 Pigmentary changes secondary to imiquimod use have been previously reported and are therefore mentioned as a possible side effect on the package.2 However, there are relatively few clinical cases available in the literature, and there is a lack of multi-year follow-up to determine the duration of depigmentation. The FDA lists 68 reports of pigmentary changes out of a total of 1,257 reports related to imiquimod from 1997 to 2003.3 In this case, we report an unusual presentation of imiquimod-induced depigmentation with nine years of follow-up, supporting the possibility that this adverse effect may be permanent.

Case Report

A 57-year-old woman presented with multiple actinic keratoses at various locations including the nose, right upper lip, and chest. She was prescribed imiquimod 5% cream to apply to the lesions Monday, Wednesday, and Friday nights. After one month, this was increased to application every night for three weeks. Five days after starting the nightly application, the patient called complaining of swelling and blistering around her lips, swelling around her eyes, and erythema where she had applied the imiquimod. She was instructed to stop the imiquimod and return to office for evaluation. On evaluation, the patient was noted to have erythema, edema, and crusting on facial and chest application sites. The patient was instructed to use petroleum jelly three times a day and continue the discontinuation of topical imiquimod. At the follow-up two months later, the patient had developed areas of depigmentation on the chest from the imiquimod. Nine years after use of imiquimod cream, the patient continues to have areas of depigmentation on her chest (Figure 1).

Discussion

Imiquimod-induced depigmentation is a rare side effect. In our case, depigmentation continued at nine years post imiquimod therapy, providing valuable insight suggesting that the depigmentation can be permanent. A literature review revealed the development of imiquimod-induced depigmentation in a limited number of previously published case reports.3-15 The nine-year follow-up in our case supports that this effect may be long-lasting and of cosmetic significance to patients.

The possible mechanism of the pigmentary changes secondary to imiquimod use relates to its properties as an immune-response modifier. Imiquimod stimulates cytokine production (interferon-alpha, interferon-gamma, and interleukin-12), thereby leading to cell-mediated immunity including anti-viral and anti-tumor activity.16,17 This creates an inflammatory reaction, such as the erythema that our patient initially experienced where she applied the imiquimod cream. Thus, the depigmentation may be analogous to post-inflammatory hypopigmentation.

Additional mechanisms may also play a role. Imiquimod may further cause depigmentation via a mechanism similar to the pathogenesis of vitiligo. Imiquimod promotes cytokine release, which results in the activation of cytotoxic T cells and antigen presentation by Langerhans cells.17 Depigmentation in vitiligo occurs with the presentation of autoantigens by Langerhans cells leading to activation of cytotoxic T cells to destroy melanocytes. Melanocytes also have increased sensitivity to the oxidative stress that may be mediated by imiquimod.18 Depigmentation may
be a result of direct effects on melanocytes. One study demonstrated that imiquimod induces apoptosis of melanocytes. Therefore, the desirable therapeutic anti-viral and anti-tumor effects of imiquimod, through a mechanism involving inflammation and Langerhans cells antigen presentation, may also lead to the undesirable side effect of depigmentation.

Imiquimod may also lead to depigmentation via its signaling of the innate immune system through toll-like receptor 7 (TLR7). Melanocytes treated with imiquimod led to reduced pigmentation, suggesting TLRs in melanocytes play a role in inflammation-related pigmentary changes.

**Conclusion**

Given that imiquimod is a commonly used therapy, dermatologists should be aware of the potential side effect of depigmentation that may be permanent. Patients should be educated about their treatment options and informed about this possible side effect before deciding whether or not to use imiquimod therapy. Alternative treatments such as cryosurgery may also result in depigmentation; in fact, in a small study comparing cryotherapy to imiquimod therapy for actinic keratosis, the cosmetic outcome was better with imiquimod, with significantly fewer patients experiencing hypopigmentation. The mechanism leading to imiquimod-induced depigmentation likely involves post-inflammatory hypopigmentation as well as immune-mediated effects on melanocytes.

**References**


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Telangiectasia Macularis Eruptiva Perstans: A Case Presentation and Discussion

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Abstract
Telangiectasia macularis eruptiva perstans (TMEP) is a rare subtype of cutaneous mastocytosis that tends to appear during adulthood. Cutaneous mastocytosis is a proliferation of mast cells limited to the skin that spares other organs. Dermatoscopy of the lesions show red-to-brown, telangiectatic macules diffusely spread over the trunk and upper extremities. We present a case of a 32-year-old male with TMEP who lacked systemic symptoms and discuss the clinical presentation, histopathology, and treatments.

Case Report
A 32-year-old Caucasian male presented complaining of new-onset skin lesions on his chest, back and left eye. He reported that the lesions began to appear about three months prior and since then had increased in number. The patient complained that the lesions felt pruritic, burning and very uncomfortable. He also reported that he had sudden onset of flushing and sweating with stress. A review of systems was negative for weight loss, constitutional symptoms, preceding illness, dyspnea, epistaxis, abdominal pain and diarrhea. Past medical and surgical history was insignificant. Family history included a first cousin on the maternal side with vitiligo and epistaxis and a mother who died of breast cancer. The patient had no known drug allergies. Physical examination revealed no visible oral mucosal telangiectasias or lesions. Cutaneous findings included multiple brown-to-red, telangiectatic macules of varying sizes diffusely placed on the body, with the majority of the lesions present on the scapula (Figures 1 and 2). The remainder of the exam was essentially normal.

A total tryptase level, CBC with differential, CMP, BMP, and thyroid-hormone level were obtained, and all were within normal limits. A 6 mm biopsy was taken from the patient’s skin overlying the right scapula. The pathology report described dilated small blood vessels within the superficial dermis (Figure 3). A Leder stain highlighted a slightly increased number of mast cells within the dermis (Figure 4).

Another 3 mm punch biopsy was taken from the patient’s lower back on the right side. The pathology report described occasional small lymphocytes and scattered mast cells (Figure 5). Leder stain highlighted approximately 18 mast cells per high power field in the papillary and superficial dermis (Figure 6).

The patient was sent for genetic testing. No abnormalities were reported.

The constellation of physical and histological features pointed toward a diagnosis of telangiectasia macularis eruptiva perstans.

Discussion
Mastocytosis is a collection of rare disorders, all caused by the pathologic proliferation of mast cells. The disorders are typically categorized into two major subtypes based on whether or not the proliferation is localized. When limited to the skin, the term "cutaneous mastocytosis" is used. If the proliferation of cells is widespread throughout the organs of the body, it is termed "systemic mastocytosis." Mast cells play a role in inflammatory and allergic responses by releasing cytokines, histamines, tryptases, interleukins and other chemical mediators upon degranulation. The downstream effects of these mediators on their receptors cause the clinical manifestations seen in mastocytosis.

Systemic mastocytosis is marked by syncope, tachycardia, pruritus, dyspnea, abdominal pain, diarrhea or flushing. Cutaneous mastocytosis, on the other hand, does not manifest with systemic symptoms. It is subdivided into four categories: urticaria pigmentosa, mastocytoma, diffuse and erythrodermic cutaneous mastocytosis, and telangiectasia macularis eruptiva perstans (TMEP). TMEP was initially described by Parkes Weber in 1930 and is found in less than 1% of patients diagnosed with cutaneous mastocytosis.

TMEP, unlike the other types of cutaneous mastocytosis, often presents in adulthood. Clinically, it is characterized by red-to-brown, telangiectatic macules. The lesions are usually...
between 2 mm and 4 mm in diameter and are commonly found on the trunk and proximal extremities, symmetrically. The palms, soles and face are classically spared. There may be variable amounts of pruritus associated with the lesions. Darier’s sign (urticaria after friction accompanied with erythema, pruritus and swelling) is commonly absent in this form of cutaneous mastocytosis, but is found in other types.

TMEP has been found in the setting of systemic mastocytosis. Suspicion of systemic involvement should arise if patients have simultaneous symptoms of anaphylaxis, dyspnea, diarrhea, syncope, tachycardia, pruritus, abdominal pain, and flushing. Tryptase is a large component of the granules contained within mast cells, and therefore measuring the total serum tryptase level is a good test to decipher if patients have systemic involvement.

Histopathologic studies of skin biopsies are used to confirm the diagnosis of TMEP. Histologically, TMEP demonstrates increased perivascular and interstitial mast-cell collections surrounding dilated telangiectatic blood vessels. The mast cells are usually located in the upper portion of the dermis, surrounding the dilated blood vessels. The number of mast cells is only slightly increased, and there may also be associated findings of epidermal hyperpigmentation.

There is no gold standard therapy for TMEP, and the goal is to alleviate symptoms. H1 antihistamine antagonists can be used to treat the pruritus and flushing symptoms, while H2 antagonists can be used in treating the gastric hypersecretion. It is important for patients to avoid triggers that can stimulate mast-cell degranulation. Triggers can include, but are not limited to: alcohol, bacterial toxins, stress, exercise, food, sunlight, temperature extremes, narcotics and anesthesia. Psoralen (oral), UVA photochemotherapy, high-dose UVA-1 and narrow-band UVB phototherapy have all been shown to improve symptoms and cosmetic appearance. Surgery via a 585 nm flashlamp-pumped dye laser has also shown cosmetic improvement in the cutaneous lesions. The replacement of antihistamine therapy with montelukast therapy was shown to be effective in the treatment of TMEP. Most of the results from treatment are temporary unless therapy is continued indefinitely. A recent study used cabozantinib, a signal transduction inhibitor that blocked growth of mast cells with the D816V codon mutation.

References

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Introduction

Pigmentary disorders are common in infants and children, often causing emotional distress to parents and providers. Hypomelanosis of Ito is an uncommon condition representing somatic mosaicism, with hypopigmented patches and streaks following the lines of Blaschko. Associated systemic findings range from none to severe systemic effects. The diagnosis is clinical, based on history and physical examination, and subsequent workup is based on associated findings. Currently, there is no treatment for cutaneous manifestations.

Case Reports

Case 1
A 4-month-old male Hispanic infant presented to our clinic with a primary concern of unusual pigmentation covering the child's entire body. The mother stated that when the infant was born, she noticed mild pigmentation changes, but by two weeks of age the pigmentation was very noticeable. The child had been diagnosed with bilateral sensorineural hearing loss, plantar flexion contractures of the feet bilaterally, ankle contractures and flexion contractures of the fingers. His pediatrician was concerned for developmental delay based on poor head control and delayed motor skills. The gestational period was uneventful, with the patient being born at term with a normal vaginal delivery. Family history was reviewed and not contributory.

On examination, the patient had whorls and streaks of hypopigmentation involving the majority of his skin surface in a blaschkolinear pattern (Figures 1 and 2). The patient had no teeth at the time of examination. Examination of the eyes revealed matching eye color and no strabismus. Head control was indeed poor, and he had stiff joints of the hands and feet bilaterally. No laboratory work or biopsies were done. Based on the child's history and physical examination, a diagnosis of hypomelanosis of Ito was made. No specific treatments were rendered, but referrals were made to a geneticist, neurologist and orthopedic surgeon for evaluation and possible treatment. Since initial evaluation, the patient has been lost to follow-up.

Case 2
A 3-month-old male Indian infant presented to our clinic for concerns of pigmentation changes. The parents stated that at birth it was undetectable, but the pigmentation became pronounced by about six weeks of age. They had tried hydrocortisone lotion as well as emollients without improvement. Beyond his skin findings, the child has been eating well and meeting all milestones. Family history was reviewed and found to be non-contributory.

Physical examination showed the ventral aspect of the child's trunk, the proximal legs and the left forearm to have hypopigmented patches following a blaschkolinear pattern (Figure 3). The remaining body surfaces had no noticeable pigmentation changes. The child did not have teeth at the time of exam. There were no noticeable musculoskeletal abnormalities, and eye examination showed matching irises. The child's case was discussed with the pediatrician and the parents, and no referrals were made. Instead, we decided to continue to monitor the child's development and make further evaluations based on potential findings as they arise.

Discussion

Hypomelanosis of Ito (HI) is an uncommon syndrome presenting as hypopigmented whorls or streaks that generally follow the lines of Blaschko. This striking physical...
and plaque-like patterns can be found.2-4 The occasional checkerboard, dermatomal, phylloid pattern represents chromosomal mosaicism in pigment production of the skin.1 The majority of cases follow the blaschkolinear pattern, but hypopigmentation is the only constant feature associated with the hypopigmentation.12 As this condition is uncommon, and many mild cases likely go unreported, it is difficult to know the true number of HI cases that have associated systemic anomalies. Nehal et al. found that extracutaneous manifestations were only present in 33% of cases, and that the severity of these symptoms was directly correlated with the level of mosaicism, as with our two patients.7

Associated findings include neurologic, musculoskeletal (MSK), dental and ocular abnormalities.5 Neurologic symptoms are most common, ranging from seizures to severe mental retardation. Musculoskeletal symptoms are also common and include abnormalities of the phalanges, limbs, spine, skull and sternum.2,6-10 Dental abnormalities include anodontia and dysplasia. Strabismus and hypertelorism have been reported. Recently, an infant was diagnosed with HI and associated pulmonary hypoplasia.11

Diagnosis is clinical, based on the cutaneous findings, but associated symptoms may help identify HI. Some authors, however, only apply the term HI when there are extracutaneous symptoms associated with the hypopigmentation.12 Alternative terms to use for patients with only cutaneous findings could be “linear nevoid hypopigmentation” (LWNH). It presents within the first year of life in 75% of patients, with lighter-skinned children sometimes presenting as late as childhood. There is a slight female predominance.3 Historically, HI had been described as incontinentia pigmenti achromians, as it appeared to be a negative image of incontinentia pigmenti, but this term has fallen out of favor because the two conditions are not related.

Table 1. Diagnostic Criteria Proposed by Ruiz-Maldonado, et al1

<table>
<thead>
<tr>
<th>Criteria 1 (must have)</th>
<th>Congenital or acquired nonhereditary cutaneous hypopigmentation in linear streaks or patches involving more than two body segments</th>
</tr>
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</table>
| Major                | 1+ nervous system anomalies  
                        | 1+ MSK anomalies |
| Minor                | 2+ congenital malformations other than neuro or MSK  
                        | Chromosomal anomalies |
| Definitive dx        | Criteria 1 and 1+ Majors, or Criteria 1 and 2+ Minors |
| Presumptive dx       | Criteria 1 alone, or Criteria 1 with 1 minor |

Table 2. Differential Diagnosis of Blaschko-linear Pigment Alteration

<table>
<thead>
<tr>
<th>Condition</th>
<th>Presentation</th>
<th>Associated Findings</th>
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| Hypomelanosis of Ito              | - Numerous genetic defects associated  
                        | - Somatic mosaicism  
                        | - Hypopigmented macules and papules that follow the lines of Blaschko  
                        | - Covers more than two dermatomes  
                        | - Often bilateral, but not symmetrical |
| Incontinentia Pigmenti            | - X-linked dominant, and deadly in males  
                        | - NEMO gene mutation  
                        | - Four stages: Newborns: linear papules and vesicles; eosinophilia Lesions progress to verrucous streaks that usually resolve 3-6 months: hyperpigmented whorls and swirls along Blaschko lines 2nd-3rd decade: hyperpigmented whorls become hypopigmented |
| Lichen Striatus                   | - Sudden eruption of erythematous or skin-toned linear papules  
                        | - Usually asymptomatic, but can be pruritic  
                        | - Active eruption lasts approximately 6-12 months  
                        | - Post-inflammatory pigment alteration common for years  
                        | - Unilateral |
| Linear and Whorled Nevoid         | - Also represents somatic mosaicism  
                        | - Hyperpigmented and hypopigmented macules that follow lines of Blaschko  
                        | - Present at birth or in infancy and continues to grow for 1-2 years, then stabilizes |
| Hypermelanosis of LWNH            | - GNAS1 mutation  
                        | - Café-au-lait macules that follow the lines of Blaschko and present in infancy  
                        | - Often unilateral  
                        | - “Coast of Maine” border of café-au-lait macule |
| McCune-Albright Syndrome          | - Multiple endocrine abnormalities  
                        | - Precocious puberty  
                        | - Polyostotic fibrous dysplasia  
                        | - Oral mucosal lentigines may present later in life |
| Focal Dermal Hypoplasia (Goltz Syndrome) | - X-linked dominant  
                        | - Mutation in PORCN gene  
                        | - Hypopigmented or hyperpigmented blaschkolinear lesions with associated dermal atrophy and telangiectasias |
                        | - Ectrodactyly (lobster-claw deformity)  
                        | - “Raspberry-like” papillomas favoring perioral and perianal area  
                        | - Ocular and dental abnormalities common |

1-10: References.
hypopigmentation” or “pigmentary mosaicism.” This naming system seems ill-conceived, though, since the true effects of subtle neurologic and extracutaneous defects may not be evident until years later, as developmental milestones and speech progress, and the eventual recognition of those defects would require a renaming of the child’s condition. We prefer to consider this a spectrum of disease and use HI to describe all patients with this phenotypic pattern.

In 1992, Ruiz-Maldonado et al. proposed criteria to diagnose HI, found in Table 1. They based the criteria on clinical experience and previous reports, though they admit the criteria may not be accurate in diagnosing HI until its etiology has been found. They categorized the presence of chromosomal anomalies as a minor criterion, and present HI as a neurocutaneous syndrome. While significant advances have been made since this classification was introduced, it may still provide useful guidance for practitioners.

Mosaicism is the presence of two genetically distinct cell lines in a single person derived from a homogeneous zygote. In embryogenesis, chromosomes are randomly distributed and migrate dorsoventrally along lines of Blaschko, resulting in two populations of epidermal skin with different pigment-producing potential. Phenotype varies greatly depending on the timing of the mutation and the cell lines affected. As would be expected, a mutation presenting earlier in embryologic development will have more widespread pigmentary mosaicism and be associated with more severe systemic findings. Mutations occurring late in development are likely more segmental and associated with absent or mild systemic findings. Our two cases seem to support this.

Multiple genetic defects have been found in patients with HI. Thomas et al. found mosaicism in lymphocytes and skin fibroblasts along with autosomal or sex chromosomes. Moss et al., however, found no dermal abnormalities but did find mosaicism within involved keratinocytes. Pascual-Castroviejo et al. recorded autosomal-dominant inheritance in some patients, but most cases appear to be sporadic. Happle et al. published a case report of sporadic inheritance in a 26-year old male. Despite the variation, four common genetic defects have been found: short arm of X-chromosome (XP11), short arm of chromosome 18, and arm of X-chromosome (XP11), short arm of chromosome 18, and arm of X-chromosome (XP11), short arm of chromosome 18, and arm of X-chromosome (XP11). In addition, failure of X-inactivation (lyonization) may be responsible for sporadic cases of HI.

Histopathologic examination could be useful if the diagnosis is in doubt, but it is not required in the evaluation of HI. Histology can show only subtle changes of fewer melanocytes and fewer, smaller melanomas that do not produce sufficient pigment. Cytogenetic analysis may reveal chromosomal mosaicism in the keratinocytes, but this test may not be available in all areas. Electron microscopy reveals fewer dendrites. None of the histologic, genetic or electron-microscopy findings are adequate to diagnose HI. Differentials for hypopigmentation that follow Blaschko lines can be found in Table 2.

Presentations of HI may vary, and it is important to perform a thorough examination to identify any concurrent musculoskeletal, neurologic, dental and ocular symptoms. Identification of hypopigmentation can be made with histology, genetic testing and Wood’s light. Once HI is suspected, optional testing includes radiography for skeletal abnormalities, electromyelography (EMG) for muscle function, head CT or MRI, ophthalmologic exam, and electroencephalography (EEG) if seizures are present. Magnetic resonance imaging appears to be the most sensitive test to visualize neural migration abnormalities. It is prudent to involve primary care, orthopedic or physical medicine specialists, and neurologists (as needed) early in the patient’s life. A referral to a geneticist is also likely warranted.

Conclusion
There are no specific treatments for hypomelanosis of Ito, but prompt identification of associated findings may improve prognosis in patients. Once identified, early involvement of a multidisciplinary team is warranted based on the extracutaneous findings. The striking physical findings are a result of pigmentary and chromosomal mosaicism, but there is still much to be learned about the genetic mutations leading to these findings. With improved knowledge, more focused workups and treatments may be available in the future.

References
Phacomatosis Cesioflammea: A Case Report of a Newborn with an Unusual Mongolian Spot and Port Wine Stain

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Abstract

Phacomatosis cesioflammea is a rare congenital cutaneous disorder that presents with aberrant Mongolian spot and port-wine stain in a newborn. About half of reported cases develop extracutaneous symptoms, especially involving the central nervous system, so early diagnosis is key in managing these patients so that appropriate referral to a specialist is promptly initiated. This case report documents the process of evaluating a newborn with an unusual Mongolian spot and port-wine stain. A thorough list of differential diagnoses, including nevus simplex, arteriovenous malformations, infantile hemangioma, Klippel-Trenaunay syndrome and Sturge-Weber Syndrome, was ruled out before ultimately diagnosing the patient with phacomatosis cesioflammea. After a year of close neurodevelopmental monitoring, the patient has not manifested any systemic complications, and his prognosis remains good.

Introduction

Phacomatosis cesioflammea is the most common subtype of a group of rare congenital cutaneous abnormalities known as phacomatosis pigmentovascularis (PPV). The Latin translation of phacomatosis cesioflammea, meaning “bluish gray” and “flame,” appropriately describes the classic appearance of congenital dermal melanocytosis (Mongolian spots) and nevus flammeus (port-wine stain). Cutaneous lesions alone are largely asymptomatic, but approximately 50% of cases have systemic involvement, which usually presents within the first months of life. For this reason, a complete physical, including a dilated ocular exam by an ophthalmologist, and close neurodevelopmental monitoring are imperative parts of management. Furthermore, keeping in mind a broad differential is prudent when diagnosing any rare disorder so as not to overlook a more common condition with similar presentation. This case report documents the process of diagnosing a newborn with phacomatosis cesioflammea and subsequent management considerations.

Case Report

A healthy term African-American male, born vaginally after an uncomplicated pregnancy to a 23-year-old G1P1, presented with unusual skin findings on initial newborn exam (Figure 1). An extensive Mongolian spot covered his right flank, buttock, and thigh (Figure 2), and a large port-wine stain extended from his chest to the fingertips of the right extremity (Figure 3). A 6 mm x 20 mm café-au-lait spot was also noted on the right lower back. Limbs were symmetric, without leg-length or limb-girth discrepancies. History and clinical exam were otherwise unremarkable. Family history was significant only for eczema in his mother. The first task at hand was to formulate a list of differential diagnoses. Vascular birthmarks such as port-wine stains are common findings in a newborn, either in the absence of or in association with congenital cutaneous syndromes. Port-wine stains are low-flow capillary malformations that present as blanchable, red or pink patches in 0.1% to 2% of newborns. Nevus simplex, also known as “salmon patch” or “stork bite,” is evident in 80% of newborns and may be similar in appearance to a port-wine stain. Unlike this patient’s vascular markings, nevus-simplex patches have indistinct borders, favor the midline such as the nape of the neck or eyelids, and resolve spontaneously. Arteriovenous malformation, another vascular cutaneous finding, may present as macular-vascular patches that generally possess a thrill and grow over time. Infantile hemangiomas, the most frequently encountered type of vascular tumor, often appear at birth as telangiectasia with surrounding pallor due to vasoconstriction. These lesions may resemble port-wine stains in early stages and then enlarge in the first few years of life before spontaneously resolving.

The prominence and unilaterality of the patient’s port-wine stain, preferentially distributed to the right upper extremity, raised concern for presence of an associated syndrome such as Klippel-Trenaunay syndrome (KTS) or Sturge-Weber syndrome (SWS). KTS is a congenital malformation of the capillary, venous, and lymphatic systems in the extremities. Cutaneous findings classically present with unilateral extremity enlargement from underlying musculoskeletal hypertrophy, visceral hemangiomas, and venous varicosities. SWS presents with facial port-wine stain, leptomeningeal capillary malformations, and central nervous system (CNS) abnormalities including seizures, mental retardation, glaucoma or neurologic deficits. Cutaneous manifestations are often progressive and...
bilateral.8 After further evaluation, KTS and SWS were placed low on the list of differential diagnoses given that the patient had no note of leg- or arm-size abnormalities and no facial rashes, and these diagnoses would not adequately explain the patient's extensive Mongolian spot.

Mongolian spots are the most common type of hyperpigmented lesions in a newborn, especially in Asian, African American, and Hispanic populations.9 These lesions are benign and present as blue-to-gray macules due to delayed disappearance of dermal melanocytes deep in the dermis. Pigment is usually located near the sacral and buttock area and fades within the first two years of life.10 Lesions located in extrasacral areas are known as "aberrant" and may raise concern for underlying disorders. For example, perioral Mongolian spots have been reported in 20% to 50% of patients with cleft lip.11 There have also been cases of persistent ventrally and dorsally distributed Mongolian spots associated with certain lysosomal-storage disorders.12

The patient was eventually given a working diagnosis of phacomatosis cesioflammea, which was later confirmed by dermatology consultation. This cutaneous disorder adequately explains the patient's unusual presentation of Mongolian spot and port-wine stain. The overall anticipated prognosis for this particular patient is good. The absence of systemic involvement is especially encouraging. Close contact has been maintained with the patient's mother and pediatrician, who report he is happy and developing appropriately. He had a dilated ocular exam per ophthalmology, which was normal, and is to follow up annually with dermatology to monitor cutaneous lesions.

Discussion
Phacomatosis pigmentovascularis, or PPV, is a group of rare congenital cutaneous abnormalities diagnosed clinically by the coexistence of pigmented nevi and vascular malformations.2 The first case of PPV was described in 1947 by Ota et al., who categorized the disorder into types I through V, with subtype "a" for cutaneous involvement only and "b" for presence of extracutaneous findings.2 In 2005, a simpler classification system was established by Happle involving four main groups: phacomatosis cesioflammea, phacomatosis spilorosea, phacomatosis cesiomarmorata, and unclassifiable PPV.2 Phacomatosis cesioflammea, or PPV type II, is diagnosed by the presence of aberrant Mongolian spots and port-wine stain. Additional cutaneous findings may include nevus anemicus (hypopigmentation due to permanent vasoconstriction), nevus of Ota (pigmentation along the first or second branches of the trigeminal nerve), cafe-au-lait macules, CNS involvement or ocular symptoms. Prognosis of the disorder largely depends on the presence of systemic disease.9

Roughly 250 total cases of PPV have been reported worldwide, with phacomatosis cesioflammea accounting for 77% of these cases.2 Studies reveal a slight female predominance8 as well as an increased incidence in Argentinian, Hispanic, and Japanese populations.13 Limited literature of twin studies in PPV strongly suggest twin discordance, in which monozygotic twins of PPV patients are unaffected.14

The pathogenesis of PPV is largely unknown. The most promising hypothesis involves "twin spotting" or didymosis, a phenomenon well-studied in plants and animals.15 Didymosis represents a specific form of somatic recombination whereby two neighboring but genetically different mutant clonal cells sporadically cross over to form distinctive homozygous cell lines.1 In the case of PPV, this process likely occurs in genes coding for vessel and melanocyte development, thus resulting in the mosaic appearance of both vascular and pigmented nevi.14

Skin lesions alone are largely asymptomatic and may lighten over time.16 However, approximately 50% of PPV cases have systemic involvement, usually appearing within the first months of life.1 Research suggests a correlation between the amount of cutaneous involvement and an increased risk for multi-systemic complications.8 The central nervous system is most commonly affected, presenting with seizures, cerebral atrophy, neurodevelopmental delay, psychomotor retardation, external hydrocephalus, stroke, and intracerebral hemorrhage.8,13,16 Common ocular findings include glaucoma, episcleral vascular malformations, conjunctival melanocytosis, primary acquired melanosis, epiretinal membrane, vitreous hemorrhage, pigmented cataracts, amblyopia, and related choroidal melanoma.12 Other complications include atrial septal defect, renal agenesis, umbilical hernia, idiopathic facial paralysis, diabetes insipidus, vitiligo, hyper IgE, IgA deficiency, pyogenic granuloma, cavernous hemangioma, scoliosis, premature tooth eruption, macrocephaly, Arnold-Chiari type I, syndactyly, bilateral deafness, and eczema. Some reports note an association with KTS and SWS.17

Initial workup should include a complete physical exam, close neurodevelopmental monitoring, and a thorough dilated ocular exam by an ophthalmologist.2 No treatment may be warranted in patients with cutaneous findings only, but for cosmetic purposes a pulsed dye laser can be used for nevus flammeus and a Q-switched laser for pigmented nevi.16 These procedures should be performed in childhood before school age for the best results.18 Evidence of extracutaneous involvement may require further evaluation with early referral and prompt treatment to optimize patient outcome.16

Conclusion
Mongolian spots and port-wine stains can be common findings on initial newborn exams. Special attention should be paid when dealing with atypical presentations of these otherwise-benign pigmented and vascular birthmarks, or if the two present simultaneously such as in phacomatosis cesioflammea. Upon diagnosis, a thorough physical exam should be performed, including a dilated eye exam by an ophthalmologist and close monitoring for signs of neurodevelopmental delay, to assess for extracutaneous manifestations.2 In patients with cutaneous findings alone, prognosis is good, and treatments such as pulsed dye laser or Q-switched laser are optional for cosmetic purposes.16 Patients with extracutaneous findings, which mainly involve the central nervous system, may require referral to a specialist for further management as indicated. While phacomatosis cesioflammea is a rarely reported disorder, physicians should keep it in mind when evaluating any newborn with prominent and unusual birthmarks.

Acknowledgments
Special thanks to the patient’s mother for her close communication and cooperation throughout the writing of this article. Thanks as well to AnMed Health Women’s and Children’s Hospital, Dr. Lorraine Bruce, Dr. Matthew Cline, Greenwood Genetics, Melanie LaVoie, Dr. Theresa Knoepp, Dr. David Malpass, and Dr. Mary K. Spraker for their contributions in providing medical care for this patient.

References


Perspectives
Views from the JAOCDD Readership
Most of us started the long, often arduous journey to become dermatologists for one reason: to help people. However, with the various complicated steps we take on a daily basis, like learning the billing, dealing with insurance companies, and memorizing the board fodder, we often forget the simple, true motivation behind what we do. I feel fortunate that my dermatology program through Western University/College Medical Center continues to instill the spirit of altruism by providing us the opportunity to serve underserved people in the global community.

Our dermatology program is the only osteopathic dermatology program in the state of California. Historically it has been led by Dr. David Horowitz, and now is being continued by Dr. Navid Nami. From day one of our dermatology residency, Dr. Horowitz reminded us of why we are doing this. He gave us a list of tips that successful people use on a daily basis to not only be successful in our dermatology residencies but also in every aspect of our lives so that hopefully, we can represent our osteopathic communities well.

One of the major lessons Dr. David taught all our residents is the importance of caring for people, not only in our local communities but also in every aspect of our lives so that hopefully, we can represent our osteopathic communities well.

Addis Ababa, Ethiopia. Here, we created our own clinic using an elementary school and saw over 1,100 patients within a week's time. Every day, we would walk into a chaotic scene where people were lined up for hours just to see us. It was an extremely rewarding experience to end each day knowing we had served each person who had waited to the best of our abilities. Along the way, we picked up some of the local language, Amharic, which to this day we try to use with the occasional Ethiopian patient we may encounter.

We also spent time volunteering at an HIV-dermatology clinic, as well as a leprosy clinic. Here we saw HIV-related dermopathy that we had only read about and were able to learn about the various stages of leprosy first-hand, as well as see the local approach to diagnosis. We saw interesting pathology, including a hemangiopericytoma on an infant's hand, X-linked ichthyosis and Madura foot. It was an amazing experience for all of us because it was the first time any of us residents had been to Africa and we were awarded the chance to meet so many interesting local people.

My second year of residency, we went to the Dominican Republic, where we served a small community in San Francisco de Marcos. Here, we traveled with the Global Health Organization and saw mainly dermatology but also primary care patients with the help of our multispecialty team. We treated a range of conditions, from mundane conditions like verruca, acne, melasma...
Our dermatology team in the Dominican Republic, led by our fearless leader in altruism, Dr. David Horowitz.

and photodermatitis to less-common entities like xeroderma pigmentosum. We also performed house calls in the local community, where we treated severe decubitus ulcers and performed hospice care.

One of the best parts of our experience was that we were able to further develop our Spanish-speaking skills by talking to patients, as well as with the help of the volunteer Dominican students who translated. Through our interaction with these Dominican students, we were able to not only have a better cultural experience but also give back further to the community as mentors, which is a role we treasure to date.

Our international dermatology experiences are one of the most cherished memories that I will take away as I graduate from residency in the next few months. We were able to not only travel to new and exotic locations but also reach many people and provide them with the medical aid they have needed for years. Dr. Horowitz’s ambition to treat patients internationally has only grown stronger as he has retired as program director; with his direction, we continue to be excited about serving abroad. We are currently planning our next medical mission to Guatemala and look forward to again embracing the philanthropic reason why we all joined this profession in the first place.
Letter to the Editor: Wegener’s Granulomatosis Eponym

David Thomas, MD, JD, EdD,* Jacqueline Thomas, DO**

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**Assistant Professor of Dermatology and Mohs Surgery, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL

To the JAOCDD Editor,

Thank you very much for the latest illuminating issue of The Journal of the American Osteopathic College of Dermatology. While all of the articles were truly worthwhile, there is some controversy concerning the eponym in the title of one of the articles, "Herpes Zoster Ophthalmicus in a Patient with Wegener’s Granulomatosis," in Volume 31, page 24. In 2008, there was a move to remove this eponym from this disease and refer to it in a more explicative form as "granulomatosis and polyarteritis."

In 1936, Dr. Friedrich Wegener described several cases of small vessel vasculitis with granulomatous inflammation.1 In 1954, Goldman and Churg described seven cases of their own and reviewed another 22 previously reported cases.2 Subsequently, the disease became known as Wegener’s granulomatosis, and that eponym has remained a fixture of the entity.

In 1989, just prior to his death in 1990, Wegener was awarded the Master Clinician award by the American College of Chest Surgeons; however, in 2007, the American College of Chest Surgeons rescinded this award predicated on Wegener’s known affiliation with the Nazi Party.3

Several authors specializing in diseases of the chest, rheumatology, and nephrology have stated that in view of that affiliation, the eponym should no longer be used.3-5

Separately, Woywodt and Matterson conducted an extensive six-year probe into the life of Dr. Wegener.5 They found that as early as 1933, he joined the Nazi Party, rising to the rank of Lieutenant Colonel and serving as the pathologist in Lodz in 1939. His office was adjacent to a Polish ghetto. They found no indication of criminal conduct on the part of Wegener, but they did uncover a letter concerning Wegener’s reviewing an article on pulmonary air embolism. Air embolism was seen in septic abortions and was a notorious finding in Nazi altitude experiments done on prisoners.

While there is no evidence of war crimes or criminal activity, the record clearly reflects Dr. Friedrich Wegener’s intimate association with and membership in the Nazi regime. As such, his character must come into question, and therefore it seems inappropriate to give him the honor of attaching his name to a disease entity. The Chest Society took the first step by removing its Master Clinician designation.

Generally speaking, we feel the practice of medicine would be well-served, and the teaching of medicine to our students enhanced, if we refrained from the use of eponyms completely and used only scientific, descriptive terminology for disease entities. While it might be awkward to refer to Starling’s Law as “End Diastolic Filling and Stroke Volume,” the descriptor, as opposed to the eponym, would not only be a far more understandable path but would also remove any potential for embarrassing ethical disclosures that might be associated with an investigator.

Yours truly,

David L. Thomas, MD, JD, EdD
Jacqueline Thomas, DO

References

Correspondence: Jacqueline A. Thomas, DO; thomasja@nova.edu
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• Children may absorb proportionally larger amounts of topical corticosteroids and thus be more susceptible to systemic toxicity. Parents of pediatric patients should be advised not to use tight-fitting diapers or plastic pants on a child being treated in the diaper area, as these garments may constitute occlusive dressings.
• Administration of topical corticosteroids to children should be limited to the least amount compatible with an effective therapeutic regimen. Chronic corticosteroid therapy may interfere with the growth and development of children.
• This medication is to be used as directed by the physician. It is for dermatologic use only. Avoid contact with the eyes.
• Patients should be advised not to use this medication for any disorder other than for which it was prescribed.
• The treated skin area should not be bandaged or otherwise covered or wrapped as to be occlusive unless directed by the physician.
• Patients should report any signs of local adverse reactions especially under occlusive dressing.
• Pregnancy Category C: Topical corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
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The following local adverse reactions are reported infrequently with topical corticosteroids, but may occur more frequently with the use of occlusive dressings (reactions are listed in an approximate decreasing order of occurrence): burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.
Save the Dates for Upcoming AOCD Meetings

2015 Fall Meeting
Loews Royal Pacific Resort at Universal Orlando
Orlando, FL
October 15-18

Thursday, October 15, 2015
8:00 a.m. - 12:00 p.m.  AOCD BOT Meeting
12:00 p.m. - 1:00 p.m.  Leaders Luncheon
1:00 p.m. - 5:00 p.m.   AOCD Program Director Meeting
8:00 a.m. - 5:00 p.m.   Exhibitor Set Up
4:00 p.m. - 8:00 p.m.  Resident In Training Exam

Friday, October 16, 2015
7:00 a.m. - 7:30 a.m.  CLIA Proficiency
7:30 a.m. - 11:30 a.m.  Lectures
11:30 a.m. - 12:00 p.m.  Break with Exhibitors
12:00 p.m. - 1:30 p.m.  Lunch Lecture
1:30 p.m. - 4:30 p.m.  Lectures
4:30 p.m. - 5:30 p.m.  Lectures
7:00 p.m.

Saturday, October 17, 2015
7:00 a.m. - 10:00 a.m.  Lectures
10:00 a.m. - 10:30 a.m.  Break with Exhibitors
10:30 a.m. - 11:30 a.m.  Lectures
11:30 a.m. - 1:00 p.m.  Lunch Lecture
1:00 p.m. - 1:30 p.m.  Break with Exhibitors
1:30 p.m. - 5:30 p.m.  Lectures

Sunday, October 18, 2015
9:30 a.m. - 12:00 p.m.  Lectures
12:00 p.m. - 1:30 p.m.  Lunch on your own
1:30 p.m. - 5:00 p.m.  Lectures
5:00 p.m.
End of Conference

*Schedule Subject to Change

2017 Spring Meeting
Ritz Carlton | Atlanta, GA
March 29 - April 2

2016 Spring Meeting
Ritz Carlton Battery Park | New York, NY
March 30 - April 3

2015 Fall Meeting
Loews Royal Pacific Resort at Universal Orlando
Orlando, FL
October 15-18
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(Journal of the American Osteopathic of Dermatology)

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