

# JAOCD

Journal Of The American Osteopathic College Of Dermatology

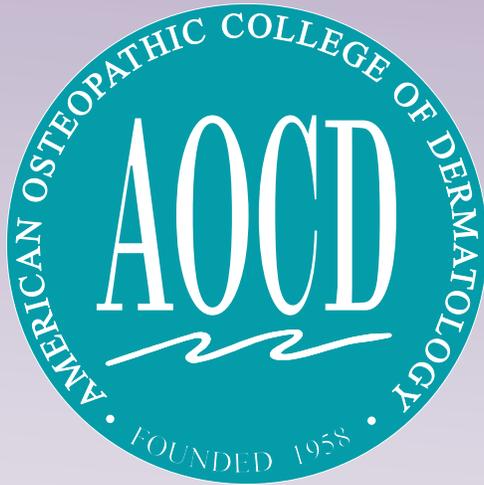
**Lymphatic Complaints in the Dermatology Clinic:  
An Osteopathic Approach to Management**  
A five-minute treatment module makes lymphatic OMT a  
practical option in busy practices.

Also in this issue:

**A Case of Acquired Port-Wine Stain (Fegeler Syndrome)**

**Non-Pharmacologic Interventions in the Prevention of Pediatric Atopic Dermatitis: What the Evidence Says**

**Inflammatory Linear Verrucous Epidermal Nevus Worsening in Pregnancy**



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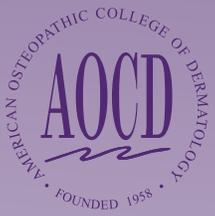
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### Citation erratum in:

Lal K, Noorollah C. "A Case of Pili Annulati Following Resolution of Alopecia Areata." J Am Osteopat Coll Dermatol. 2015;34:43.

Information in the final two paragraphs preceding the Conclusion was sourced from reference 18 (Castelli et al., 2012), not reference 17 (Smith et al., 1995) as originally published.



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# LETTER FROM THE ASSISTANT EDITOR



**Julia Layton, MFA**  
**Assistant Editor, JAOCD**

Dear JAOCD Reviewers,

Thank you for all you do.

I've been meaning to say that for a long time. I interact with some of you via email, and I get the chance to express my thanks then. (I hope I always remember to do that.) But in most cases, I only know you through your reviews, and you only know me as a name on automated emails. You may not know how much Dr. Krishnamurthy and I value you and your contributions to the journal.

As a peer-reviewed publication, the JAOCD couldn't exist if you didn't volunteer your time and expertise. In many cases, your reviews are exceptionally thorough and attentive, and some of you turn them around in a day or two. You might then review a revision. And you do all of this in what I'm guessing is precious little free time.

I know the review process can at times be cumbersome, and I'm working to refine it. I've made a couple of changes in the last six months in response to suggestions by Dr. Scott Lim. I implemented red-lining in manuscript revisions to make it easier to spot changes, which I hope is working out well. If I let a non-red-lined revision slip through, please let me know and I'll send it back to the author.

I also *think* I removed the Overall Manuscript Rating field from the review form (Editorial Manager can be an enigma.) Lack of standardization decreased its usefulness, and rather than establish rating standards and ask you to get familiar with them, I decided to let it go. Your Revise/Accept recommendations and the notes you provide the authors are what's most important.

Along those lines, remember that if you want to tell me something brutally honest about a paper, you can use the "Notes to Editor" field. Authors can't see those comments.

In other news, I have completed our second application for MEDLINE indexing, and we're on the agenda to be reviewed at the June meeting of the National Library of Medicine's Literature Selection Technical Review Committee. According to the NLM, only about 12 percent to 15 percent of journals are accepted at each meeting, so it's a rigorous process, but we're hoping the second time's the charm.

If you have ideas about how to improve the review process and/or the journal in general, please don't hesitate to let me know. I'm always available at [JuliaJAOCD@Gmail.com](mailto:JuliaJAOCD@Gmail.com).

Again, thank you for your commitment to making the JAOCD a high-quality, peer-reviewed journal that shares reliable and valuable insights. We couldn't do it without you.

Warmly,

Julia Layton

Assistant Editor, JAOCD

# LETTER FROM THE EXECUTIVE DIRECTOR



**Marsha Wise**  
**Executive Director, AOCD**

Hello, Everyone,

We've had a busy start to the year. We just returned from our spring meeting in New York City, and the reviews coming in from the conference have been outstanding. It will be time for our fall meeting before you know it. Join us at the Loews Hotel in Santa Monica, CA, September 14-18, 2016. Online registration and hotel information is available on our web site. Remember to log in with your username and password to get the AOCD member rate.

The AOCD is now in the process of applying for initial accreditation with the Accreditation Council for Continuing Medical Education (ACCME). Once obtained, the AOCD will be able to grant AMA CME in addition to AOA CME. The staff and I are excited to get this project completed for the membership.

Speaking of CME, the 2016-2018 CME guide for physicians is now available online at <http://www.osteopathic.org/inside-aoa/development/continuing-medical-education/Pages/cme-guide.aspx>. AOCD members must earn 120 CME credits for membership in the American Osteopathic Association within this three-year cycle, beginning Jan. 1, 2016 and ending Dec. 31, 2018. Of this total, 30 CME credits must be Category 1A, and the remaining 90 CME credits may be Category 1A, 1B, 2A, or 2B.

AOA Category 1A credit is granted for formal face-to-face programs that meet the Category 1 quality guidelines and faculty requirements and are sponsored by AOA-accredited Category 1A CME sponsors. The AOCD is an accredited Category 1A sponsor for Dermatology CME.

To maintain your specialty certification, you must earn a minimum of 50 specialty CME credits in each primary specialty held (e.g., Dermatology) during the three-year CME cycle. For Dermatology, as required by the AOBD, at least 25 of the required 50 specialty credits must be Category 1A.

We are happy to share the results of the recent American Academy of Dermatology's by-laws amendment vote. The vote, which passed with 69.42% voting in favor, will allow osteopathic physicians certified by the American Osteopathic Board of Dermatology (DOs) into the Fellow membership category of the AAD.

We want to stress to our members that this is only a status change. Both the AAD and the AOCD remain separate organizations and offer unique services to their respective members.

We continue to offer informational updates to our members via the Thursday Bulletin. When the bulletin arrives in your inbox, be sure to take a moment to review it. We include reminders and updates on pertinent information as often as possible.

Thank you for your continued support of the AOCD. Please call or email the AOCD office (800-449-2623, [dermatology@ao.cd.org](mailto:dermatology@ao.cd.org)) if you need assistance or have questions or concerns.

Sincerely,  
Marsha Wise  
Executive Director, AOCD

# LETTER FROM THE PRESIDENT



**Alpesh Desai, DO, FAOCD**  
**President, AOCD**

Greetings from Houston, Texas!

As I think about our recent past and the dramatic changes afoot, I recall Suzanne Sirota Rozenberg, DO, FAOCD, past president of the AOCD, commenting in a 2014 issue of the JAOCD about the future merger of the AOA and ACGME. As I've quoted previously, "Today, at this moment, we are living in yesterday's future." Our future has arrived.

The AOA, along with the Accreditation Council for Graduate Medical Education and the American Association of Colleges of Osteopathic Medicine, have agreed to a single accreditation system for graduate medical education programs in the United States. Graduates of osteopathic institutions will complete their residency and/or fellowship education in ACGME-accredited programs and demonstrate achievement of common milestones and competencies side by side with graduates of allopathic medical schools. I hope you grasp the full meaning of what you just read: Osteopathic and allopathic graduates will no longer be divided.

Perhaps the most exciting news to share is the AAD vote that just passed last month. Osteopathic physicians certified by the American Osteopathic Board of Dermatology will now be recognized as Fellows in the AAD. We have been fighting this battle for generations. The vote suffered defeat in 2004 and 2010. On both occasions, a majority of the membership voted in favor, but the two-thirds majority required to approve a change to the bylaws fell short. I was told I would never see this vote go through in my lifetime. The shift exemplifies what we all have known for a long time—we are equals with our MD counterparts. This vote gives us the ability to hold offices and serve on committees. I sincerely hope we all serve the AOCD and AAD in some capacity. By harnessing the strength of both organizations, we can affect change.

However, our work is far from done! More than ever, the preservation of our osteopathic roots is critical. The AOCD remains a strong organization. I am proud of our heritage and mindful of the work that lies ahead. This college has nurtured me throughout my career and will do the same for generations of osteopathic dermatologists to come—if we believe in and support it. The AOCD brought us to where we are. Each of us emerged as dermatologists in part because of this great organization.

The AOCD will remain a strong provider of service and support to dermatologists who chose osteopathy for their medical training and philosophy. Our boutique organization is special. Our members are not lost among the masses. Our professional development will remain world-class. Our publications will continue to disseminate valuable information and updates. The person-to-person connection is what makes AOCD one of the greatest assets in our daily professional lives.

As you read this issue, reflect on how fortunate we are to be osteopathic dermatologists. Our future will remain strong as long as we join together in keeping the vision alive, provide outstanding training and seminars to our members and never forget that our purpose is to serve patients.

I look forward to seeing you in Santa Monica!

Alpesh Desai, DO, FAOCD

President, American Osteopathic College of Dermatology

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DIAGNOSTICS

# Lymphatic Complaints in the Dermatology Clinic: An Osteopathic Approach

Bridget E. McIlwee, DO,\* Jenifer R. Lloyd, DO,\*\* Michael P. Rowane, DO, MS, FAAFP, FFAO\*\*\*

\*Dermatology Resident, OGRE-3, University of North Texas Health Science Center/TCOM, Fort Worth, TX

\*\*Director, Dermatology Residency Program, University Hospitals Regional Hospitals; Department of Dermatology, Case Western Reserve University, Cleveland, OH

\*\*\*Associate Clinical Professor of Family Medicine and Psychiatry, Case Western Reserve University; Director of Medical Education, University Hospitals Regional Hospitals; Director of Osteopathic Medical Education, University Hospitals Case Medical Center, Cleveland, OH

## Abstract

The number of patients presenting to dermatologists with lymphatic complaints continues to grow, given our aging population and the increasing prevalence of predisposing chronic medical conditions. Sequelae may include pain, stasis skin changes, and chronic wounds. Lymphatic conditions impose a physical and psychological burden on patients, as well as a financial strain on both patients and the medical system. The medical community is in need of cost- and time-effective treatment measures. Osteopathic dermatologists are uniquely suited to meet this need through our training in osteopathic lymphatic manipulative treatment techniques. These techniques are suitable for use as primary or adjunct treatments for lymphatic dysfunction. However, in a busy dermatology clinic, lengthy osteopathic treatments are often seen as impractical. A five-minute osteopathic lymphatic manipulative treatment technique module has been developed for the management of lower extremity lymphatic complaints and is appropriate for use in the general dermatology clinic.

## Definition and Epidemiology

Dermatologists are seeing an increasing number of patients who present with complaints related to lymphatic dysfunction. This is largely due to an aging U.S. population and the increasing prevalence of chronic medical issues which, either through their own natural history or due to the therapies required to treat them, predispose patients to acquired lymphatic dysfunction.

For example, an estimated 6 million to 12 million Americans suffer from peripheral vascular disease (PVD). Depending on the severity of their PVD, 30% to 80% of these individuals (approximately 2 million to 5.4 million people) will go on to suffer from resultant lymphedema.<sup>1-4</sup> Another common cause of acquired lymphatic dysfunction is surgical lymph node dissection (LND) performed in the course of cancer treatment. After LND, approximately 15% of patients go on to develop lymphedema. In patients undergoing inguinal or pelvic lymph node dissection, the incidence of resultant lymphedema may be as high as 40%.<sup>5</sup>

## Presentation and Pathophysiology

Edema and lymphedema, while potentially similar in clinical presentations and possible sequelae, differ in epidemiology and pathophysiology. Edema is defined broadly as an excess of interstitial fluid that overwhelms lymphatic drainage capacity. It is not usually clinically apparent until the interstitial fluid volume has increased ~100% to a total volume of 2.5 L to 3 L.<sup>6</sup> In order for edema to occur, one or more alterations in physiologic Starling forces must occur (see **Table 1**). Any combination of alterations in the Starling factors may result in a quicker or more severe presentation.

In contrast to edema, which is largely a secondary result of primary physiologic changes, lymphedema is a true failure of the lymphatic system, causing drainage capacity to fall below normal. Lymphedema is divided into two groups, primary and secondary, based on the etiology of the disorder (see **Table 2**).

Lymphedema can be distinguished from edema by (1) causative factors, (2) a duration of greater

than three months or (3) clinical characteristics of lymphedema such as *peau d'orange* or woody appearance of the skin and severely limited or absent pitting (see **Table 3**).

In the developed world, lymphedema is most commonly seen after surgical treatment for a malignancy, a classic example being upper extremity lymphedema secondary to surgical

lymph node dissection during diagnosis of breast cancer. Lymphedema may also be seen after severe or prolonged cellulitis. Worldwide, filariasis (caused by *Wuchereria bancrofti* or *Brugia malayi*) is the most common cause of secondary lymphedema.<sup>10</sup>

## Treatment

**Table 1. Derangements in Starling forces: physiologic and medical causes of edema.<sup>9</sup>**

<b>Increased capillary hydraulic pressure</b>
Renal sodium retention
Heart failure
Renal sodium retention: renal failure, drugs, refeeding syndrome, cirrhosis
Pregnancy
Sodium or fluid overload
Venous obstruction
Cirrhosis
Acute pulmonary edema
Local venous obstruction (e.g., DVT)
Due to vasodilation, as in lower extremity venous dysfunction
<b>Increased capillary permeability</b>
Diabetes mellitus
Burns
Hypersensitivity reactions
Sepsis or inflammation
Malnutrition
Envenomation
<b>Increased interstitial oncotic pressure</b>
Lymph node dissection
Hypothyroidism
Malignant ascites
<b>Decreased plasma oncotic pressure</b>
Liver disease
Malnutrition
Nephrotic syndrome
Protein-losing enteropathy

**Table 2. Causes of primary and secondary lymphedema<sup>7,8</sup>**

PRIMARY LYMPHEDEMA	SECONDARY LYMPHEDEMA
<i>Primary lymphedema is due to inborn aplasia, malformation, or other dysfunction of lymphatics.</i>	<i>Secondary lymphedema is caused by an acquired defect in the lymphatic system.</i>
<p><b>SPORADIC:</b></p> <ul style="list-style-type: none"> <li>The most common type of primary lymphedema.</li> <li>May occur as a feature of other sporadic syndromes, e.g., Klippel-Trenaunay syndrome</li> </ul> <p><b>CONGENITAL:</b></p> <ul style="list-style-type: none"> <li>Milroy's disease – FLT4/VEGFR3 mutation</li> <li>Lymphedema-distichiasis syndrome – FFOX2 mutation               <ul style="list-style-type: none"> <li>Delayed onset (postpubertal)</li> </ul> </li> </ul> <p><b>FAMILIAL:</b></p> <ul style="list-style-type: none"> <li>5-10% of all primary lymphedema</li> <li>Meige's disease</li> </ul> <p><b>AS A FEATURE OF OTHER INHERITED SYNDROMES:</b></p> <ul style="list-style-type: none"> <li>Turner syndrome – karyotype 45,X</li> <li>Noonan syndrome – PTPN11 mutation</li> <li>Proteus syndrome – AKT1 mutation</li> <li>Agenaes (cholestasis-lymphedema) syndrome</li> <li>Hennekam (lymphangiectasia-lymphedema) syndrome               <ul style="list-style-type: none"> <li>Type I – CCBE1 mutation</li> <li>Type II – FAT4 mutation</li> </ul> </li> <li>Hypotrichosis-lymphedema-telangiectasia syndrome – SOX18 mutation</li> <li>Microcephaly-lymphedema-chorioretinal dysplasia – KIF11 mutation</li> </ul>	<p><b>CAUSES:</b></p> <ul style="list-style-type: none"> <li>Filariasis</li> <li>Malignancy and cancer treatment</li> <li>Morbid obesity</li> <li>Trauma</li> <li>Peripheral vascular dysfunction or surgery</li> <li>Congestive heart failure</li> <li>Burns</li> <li>Recurrent infections</li> <li>Portal hypertension</li> </ul>

**Table 3. Clinical characteristics of edema and lymphedema.<sup>22,23</sup>**

Lymphedema	Edema
Duration > 3 months	Duration < 3 months
Hyperkeratosis and tissue fibrosis: hardened, hyperpigmented subcutis → <i>peau d'orange</i> or woody appearance of the skin	Generally normal-appearing epidermis; hyperpigmentation may be present
Non-pitting or severely limited pitting	Pitting

Lymphedema and edema treatment regimens focus largely on modifying physiologic factors either responsible for (in edema) or complicating (in lymphedema) lymphatic dysfunction. In milder cases of edema, lifestyle changes are often recommended. These simple adjustments, made by patients in their own day-to-day lives, may play a large role in ameliorating lymphatic dysfunction. Common interventions include weight loss, increasing daily exercise, and elevating edematous extremities when at rest. These and other, similar lifestyle adjustments can improve fluid return to the heart and significantly decrease lymphatic congestion.

In many cases of edema, first-line therapy focuses on treating an underlying medical condition. For example, in heart failure patients, interventions might include a low-salt diet and oral diuretic therapy. For patients with end-stage renal dysfunction or other fluid overload, dialysis is critical. For burn or septic patients, therapy focuses on treatment of the primary medical condition and resulting systemic inflammatory response syndrome. Similarly, for patients with edema caused by cirrhosis or deep vein

thromboses, medical treatment of the underlying condition often significantly improves or even resolves coexisting edema.

In cases of inherited or iatrogenic lymphatic dysfunction, or in those cases of edema that persist despite lifestyle changes and medical treatment, consistent use of compression stockings is a critical part of therapy. Specially-trained physical therapists may prescribe patients a specific set of exercises shown to improve lymphatic flow. Physical therapists may also treat patients with manual lymphatic drainage, or MLD. When compression stockings are used concurrently with MLD, the combination is known as decongestive lymphatic therapy (DLT).<sup>11</sup>

### Osteopathic Perspective

Both edema and lymphedema may have significant sequelae including pain, skin changes, vascular complications, and chronic wounds – all of which are common complaints in the dermatology clinic. These sequelae pose not just a physical and psychological burden to patients, but also a financial stress on both the patient and the U.S. medical system. In fact, in the United

States, an estimated \$25 billion is spent each year on the treatment of chronic wounds alone.<sup>3</sup>

Given the increasing prevalence and cost of lymphatic dysfunction both in the country and the dermatology clinic, there is a need for cost- and time-effective treatments. Lymphatic osteopathic manipulative treatment (OMT) techniques are very similar to those utilized by physical therapists trained in MLD and DLT. OMT lymphatic techniques are taught in every U.S. college of osteopathic medicine, making osteopathic dermatologists uniquely suited to address the growing challenge of lymphatic dysfunction.<sup>12</sup> Various osteopathic manipulative treatment techniques have been shown useful in the practice of dermatology; however, undertaking lengthy lymphatic osteopathic manipulative treatments in a busy dermatology clinic is rarely considered realistic.<sup>13,14</sup> Furthermore, and perhaps more troubling, in recent original research, only 5% of surveyed osteopathic medical students felt that osteopathic manipulative treatment techniques had utility in the lymphatic and vascular domains of clinical dermatologic care.<sup>15</sup>

Osteopathic manipulative treatment of lymphatic

dysfunction fits best into the respiratory-circulatory model of osteopathic principles and practices, which emphasizes normalization of a patient's pulmonary and cardiovascular functions as well as the circulation of fluids such as blood, lymph, and cerebrospinal fluid. Specifically, here we focus the application of this osteopathic model on the physiologic movement of vital fluids through the vascular and lymphatic systems, the flow of which can be impeded by restrictions in the transverse diaphragms of the body. These diaphragms include the cerebellar tentorium, the thoracic inlet, the respiratory/abdominal diaphragm, the pelvic diaphragm, and the popliteal fossa.<sup>16,17</sup>

### Osteopathic Manipulative Treatment

The authors describe a brief yet comprehensive lymphatic osteopathic manipulative treatment module, conducive to completion in a typical clinical exam room. The patient remains supine for the entirety of the module, eliminating the time and effort spent having a patient transition between several different positions during treatment. This treatment protocol is designed to be completed in five to 10 minutes, making it well-suited even for busier clinics.

In this setting, the goal of using OMT is two-pronged: first, to decrease restriction in the transverse diaphragms of the body, and second, to utilize active and/or passive oscillatory movements to encourage mobilization of lymphatic fluid from peripheral tissues and return it to the heart.

In this treatment module, the majority of the osteopathic manipulative treatment techniques utilized to modulate transverse physiologic diaphragms are myofascial release (MFR) maneuvers. The Educational Council on Osteopathic Principles defines MFR as "a system of diagnosis and treatment first described by Andrew Taylor Still and his early students, which engages continual palpatory feedback to achieve release of myofascial tissues." MFR techniques have also been defined as those "designed to stretch and reflexively release patterned soft tissue and joint-related restrictions."<sup>19</sup>

MFR can be performed as a direct or an indirect technique. Direct techniques are those in which the restrictive barrier is engaged and a final clinician-directed force is applied in order to correct somatic dysfunction. Indirect techniques are those in which the restrictive barrier is disengaged and the dysfunctional structure moved away until tension is normalized and equal in all planes of movement. Other osteopathic manipulative treatment techniques utilized in this module are of the oscillatory lymphatic type. These techniques involve passive mechanical movements, undertaken by the physician, intended to remobilize the patient's peripheral lymphatic fluid and encourage recirculation thereof.<sup>18-21</sup>

In order to most successfully decrease peripheral edema, osteopathic manipulative treatment techniques aimed at reducing transverse diaphragm restriction should be completed in a cephalad to caudad progression. This approach

first reopens proximal lymphatic pathways, allowing fluid mobilized distally to follow an unimpeded path of return to the heart.

The thoracic outlet is an anatomic space created by the boundaries of the first thoracic vertebra (T1), the first ribs, the costal cartilage of the first ribs, and the superior manubrium. If the physiologic function of the outlet is impeded, it can prevent effective return to central circulation of lymphatic fluid from both the upper extremities and the lower body. In order to ensure lymph returning from the peripheral body has a clear pathway to the circulatory system, the MFR thoracic inlet release technique should be performed. It may be undertaken as a direct or an indirect technique, first by placing the physician's hands over the thoracic inlet with the thumbs on the transverse process of T2 and the head of the 2nd rib, and the fourth and fifth fingers between the clavicle and the first rib. Thoracic inlet tissues should be moved in the direction of restriction (direct) or of ease (indirect) until an inherent release in the tissues is felt. The physician may also modify the technique into a more active form by following release through patient exhalations (**Figure 1**).

In order to encourage return of lymphatic fluid from the thorax, the oscillatory lymphatic Miller Pump is utilized. There are several variations on the performance of this technique, the most basic of which involves the physician placing hands on the patient's thoracic wall, fingers spread, with the thenar eminence just distal to clavicle. The patient turns his or her head to the side. As the patient breathes in and out, an oscillatory pressure is applied to the ribcage throughout the respiratory cycle (**Figure 2**).

In order to ensure that lymphatic fluid mobilized from the lower extremities can return cephalad, physiologic function of the transverse abdominal diaphragm can be restored via redoming. In this technique, the physician grasps the patient's abdomen with thumbs beneath the inferior costal margins. The physician then asks the patient to breathe in; as the diaphragm descends, inferior motion is resisted. As the patient breathes out, the diaphragm's cephalad motion is augmented until a tissue release is felt. The physician repeats this technique, advancing laterally along the inferior costal margins for several cycles to treat the entire anterolateral respiratory diaphragm (**Figure 3**).

The pelvic outlet is an anatomic space created by the borders of the pubic arch, the ischial tuberosities, the inferior margin of the sacrotuberous ligament, and the tip of the coccyx. The pelvic floor is made up of the levator ani and coccygeus muscles and their associated connective tissue. It spans the area underneath the pelvis and is another transverse diaphragm that, if restricted, can impede peripheral lymphatic fluid return to central circulation. To restore proper physiologic function to the pelvic outlet and floor, MFR techniques can be employed. Ordinarily, the innominate move more easily in opposing directions. The physician contacts both of the patient's iliac crests with his or her hands, simultaneously assessing position and motion of



Figure 1. Thoracic inlet release (MFR)

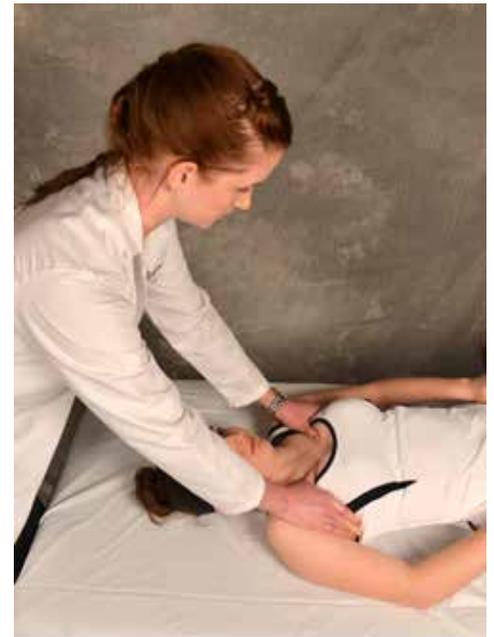


Figure 2. Miller thoracic pump (oscillatory lymphatic)



Figure 3. Redoming the abdominal diaphragm (MFR)



Figure 4. Pelvic floor and pelvic outlet (MFR)

the crests in a transverse plane. The physician positions both innominates in the direction of freer motion, balancing both sides; this position is held until a release is felt. Motion of the iliac crests is then reassessed for appropriately balanced reciprocal motion (Figure 4).

The lower extremities are common sites of lymphatic somatic dysfunction. Aside from physiologic factors, gravity also encourages lymph pooling in the feet and distal legs. Lymph return from the lower extremities can be improved in two steps: first, by encouraging effective lymph passage cephalad by relieving restriction in the popliteal fossae; and second, by inducing cephalad motion of pooled peripheral lymph via physician-induced oscillatory motion. Popliteal spread is an MFR technique in which the physician bends the supine patient's knee to approximately 90 degrees. The physician may place the patient's foot between the physician's knees or legs for support. The physician places his or her finger pads in the patient's popliteal space, applying a direct fascial spread until a release of the tissues is felt (Figures 5a, 5b).

To encourage lymphatic return to the heart, the oscillatory lymphatic pedal pump technique is employed. This technique can be utilized by inducing dorsiflexion or plantarflexion of the patient's feet; the two motions may also be employed one after another for enhanced lymphatic mobilization. The physician grasps the patient's feet with the palms contacting the MTP area of the soles. Dorsiflexion is induced, stretching the posterior body wall fascia. The physician introduces a quick further cephalad force, then releases it. This force sends a wave of tissue and therefore fluid motion cephalad, followed by a caudal rebound wave. As the rebound wave reaches the patient's feet, the physician induces another dorsiflexion force. Frequency is therefore tailored to the patient, but it generally falls within the range of 80 to 120 per minute. The duration of this treatment should be one to two minutes (Figure 6).

### Contraindications

The efficacy of lymphatic techniques has been documented in the scientific literature, and to date no significant complications resulting from lymphatic osteopathic manipulative treatment have been reported. Therefore, the risk-to-benefit ratio for the performance of lymphatic OMT is quite good, and the majority of contraindications – absolute or relative – are theoretical in nature.<sup>19</sup>

Contraindications to lymphatic OMT are often summed up by the acronym "RIFT": radiculopathy, infection (abscess in area being treated or a systemic infection with temperature greater than 102°F), osseous fracture, or tumor. Anuric patients who are not being dialyzed and patients with necrotizing fasciitis should not be treated with lymphatic OMT. Patients with systemic coagulopathies should be treated with caution, and patients with a localized coagulopathy (embolus, deep vein thrombosis) should not be treated with lymphatic OMT.<sup>13,19,24-25</sup>

The use of OMT in patients with malignancies is controversial. There is a question of whether lymphatic OMT could mobilize malignant cells, encouraging metastasis. The alternate school of thought maintains that lymphatic OMT might enhance delivery of malignant cells to the immune system, enhancing recognition and destruction. Deleterious effects secondary to the use of lymphatic OMT in patients with malignancies have not been documented; however, there is a dearth of scientific studies on the topic. Thus, these techniques should be used at the discretion of the practicing physician.<sup>19,25</sup>

In the past, some have questioned whether the use of lymphatic OMT in patients with congestive heart failure (CHF) or other causes of decreased cardiac output could result in central fluid overload and cardiovascular collapse. This concern is not supported by the literature. *In vivo* studies on terminal CHF patients showed cardiovascular stabilization after performance of thoracovenous shunting, which mimics the hemodynamic changes anticipated after performance of lymphatic OMT.<sup>26</sup> Furthermore, *in vivo* studies in canines have shown that cardiac output and heart rate, though increased during physical activity, did not change significantly during or after the use of lymphatic osteopathic manipulative techniques.<sup>27</sup> Lymphatic OMT has also been used with excellent results in coronary artery bypass graft (CABG) surgery patients during the immediate post-operative period. As compared to non-OMT-treated post-CABG control subjects, post-CABG patients treated with lymphatic OMT experienced statistically significant differences in decreased central blood volume (suggesting improved peripheral circulation), increased venous oxygen saturation, and improved cardiac index.<sup>28</sup> Thus, the use of lymphatic OMT in patients with CHF -- even if severe -- does not likely pose a risk of fluid overload, and, in fact, likely encourages hemodynamic stabilization.<sup>19,24-29</sup>

### Conclusion

Lymphatic dysfunction is a condition with serious medical, psychological, and financial implications. Its prevalence continues to rise within the United States and throughout the world. Because lymphatic dysfunction often results in skin-related sequelae, dermatologists see many patients with lymphatic complaints and secondary complications. Due to our training in lymphatic osteopathic treatment and our dedication to holistic care of our patients, osteopathic dermatologists and all osteopathic physicians are uniquely equipped to treat patients with lymphatic dysfunction. This module presents a comprehensive, effective means by which osteopathic physicians can treat patients with lymphatic complaints as a part of a routine office visit. In this way, osteopathic physicians not only improve our patients' quality of life, but also play an important role in decreasing the morbidity and health care costs associated with lymphatic dysfunction.



Figure 5a

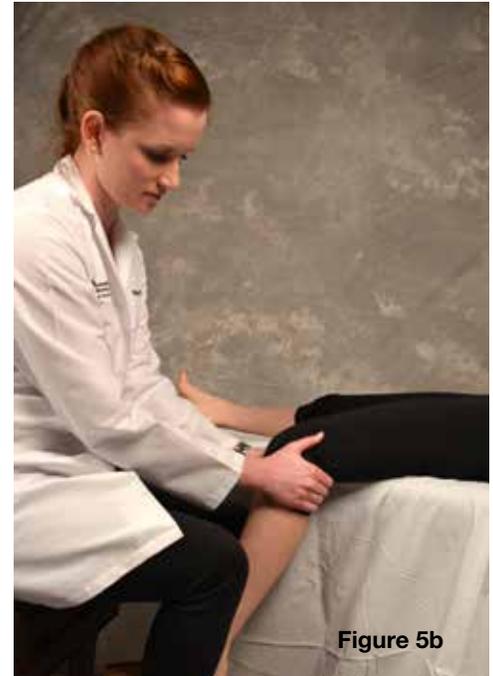


Figure 5b

Figure 5a – 5b. Popliteal spread (MFR)

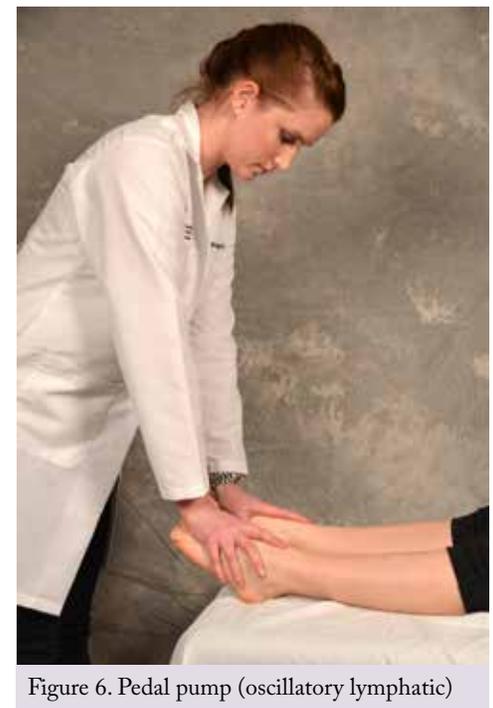


Figure 6. Pedal pump (oscillatory lymphatic)

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**Correspondence:** Bridget E. McIlwee, DO, University of North Texas Health Science Center, 855 Montgomery Street, 5th Floor, Fort Worth, TX 76107; Ph: 817-735-2922; F: 817-735-5022; [bridget.mcilwee@unthsc.edu](mailto:bridget.mcilwee@unthsc.edu)

# Acquired Port-Wine Stain (Fegeler Syndrome): A Case Report and Literature Review

J. Hibler, DO,\* Oben Ojong, BS,\*\* Benjamin H. Kaffenberger, MD\*\*\*

\*Dermatology Resident, 3<sup>rd</sup> year, O'Bleness Memorial Hospital, Athens, OH

\*\*Osteopathic Medical Student, 2<sup>nd</sup> year, Ohio University Heritage College of Osteopathic Medicine, Athens, OH

\*\*\*Dermatologist and Clinical Instructor, Ohio State University Wexner Medical Center, Columbus, OH

## Abstract

*Acquired port-wine stains are a type of capillary malformation rarely reported in the literature. Most documented cases are idiopathic in nature or caused by physical trauma. We describe a case of a 61-year-old man with an acquired port-wine stain in the left V1 distribution with ipsilateral ophthalmic findings, and hereby recommend an ophthalmologic exam for patients who present with acquired port-wine stains in the V1 trigeminal distribution.*

## Introduction

Port-wine stains (PWSs) are cutaneous capillary malformations, also known as nevus flammeus, nevus simplex or salmon patch, and are usually considered congenital vascular lesions. First described by Fegeler in 1949, *acquired* PWSs are exceedingly rare but have been previously reported and documented.<sup>1</sup> A recent literature search revealed that fewer than 100 of these lesions have been described.<sup>2</sup> Most cases are idiopathic, but trauma may be a precipitating factor.<sup>3-5</sup> Whether congenital or acquired, PWSs usually present as irregularly bordered, violaceous-to-red patches and plaques, many of which follow the V1 or V2 distribution. Congenital PWSs result from abnormal vessel development during embryogenesis, with histopathology revealing an increased number and ectasia of blood vessels in the dermis.<sup>6</sup> Herein, we present a case of an acquired port-wine stain, also known as “Fegeler syndrome,” and a review of the literature.

## Case Report

A 61-year-old Caucasian male presented after being referred for ongoing rosacea around his left forehead, eye and nose. The patient gave a history of the “rash” appearing suddenly one morning about 19 years ago. He could not account for any sort of precipitating factor such as trauma to the area, recent infections, or new medications. He described the lesions as being occasionally pruritic and slightly painful, which became more noticeable with sweating. The patient had no history of shingles.

Dermatologic exam showed a patchy and somewhat coalescing, red-pink, vascular-like lesion that extended from the left eyebrow to the distal left nasal tip and involved the inferior left eye and cheek region (**Figure 1a**). Previous ophthalmologic examinations revealed periorbital hemangiomas, with vision changes consistent with increased intraocular pressure; and blurred vision and brown tint in the left eye for approximately eight months. Also described were benign, age-related ophthalmologic findings. His surgical, family and social history were non-contributory.

A punch biopsy from the left nasal sidewall was taken, and histopathologic exam revealed a vascular lesion with associated vascular ectasia in the surface (**Figure 2**, H&E). The vessels were lined by flattened endothelial cells, some of which showed slight hyperchromasia, while others showed a thickened vascular wall. No infiltrative pattern of the lesion was seen. No mitotic figures were present. A CD34 immunostain was positive in the endothelial lining of the vessels. D2-40 was negative in the lesional cells, ruling out the presence of lymphatic cells. A diagnosis of a vascular proliferation consistent with a port-wine stain was made.

Our patient successfully underwent two treatments with a V-beam pulsed dye laser (PDL) set at: spot size: 7 mm<sup>2</sup>, fluence: 13J/cm<sup>2</sup>, pulse duration: 1.5 msec. He showed much improvement (**Figure 1b**) after two treatments and is scheduled for two more PDL sessions.

## Discussion

The pathogenesis of acquired PWS is not

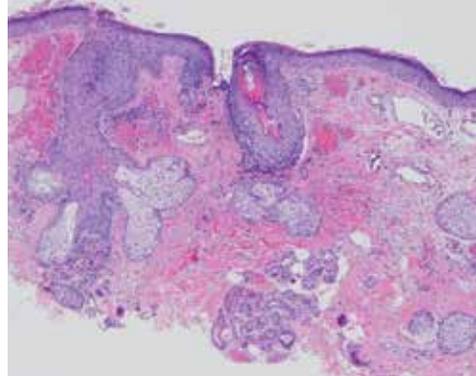


Figure 2. A punch biopsy from the left nasal sidewall.

completely understood. A history of trauma is given in approximately half of all documented cases. Our patient denied any prior trauma. Whether idiopathic, trauma-related, or from other proposed causes, the exact reason these vascular malformations become chronic and sometimes lifelong lesions has yet to be elucidated. One hypothesis points to non-proliferative vascular ectasia due to a defect in nerve fibers associated with these blood vessels, resulting in decreased sympathetic tone.<sup>7</sup> They may also be associated with malformations at the post-capillary venule.<sup>8</sup> Other studies suggest abnormalities in blood-vessel connective tissue and associated nerve supply.<sup>9</sup>

While it is known that patients with certain vascular lesions, such as infantile hemangiomas, may have other organ systems involved (e.g., hepatic), little is known about systemic involvement in acquired PWSs. There are many known syndromic diseases featuring congenital PWSs with a constellation of other organ systems involved (Sturge-Weber syndrome, Klippel-Trenaunay syndrome, Proteus syndrome, phakomatosis pigmentovascularis, and possibly tuberous sclerosis), but none so far are associated with acquired PWSs. The patient described in this case did have some ocular involvement, as his PWS involved the lower eyelid. He also had ipsilateral ophthalmic findings, including a posterior vitreous detachment (PVD) and an epi-retinal membrane (ERM). PVD is insidious



Figure 1a



Figure 1b

and asymptomatic, but it may lead to more serious macular and optic disc disease.<sup>10</sup> ERM is also a benign ocular condition but may lead to visual impairment and necessitate retinal surgical intervention.<sup>11</sup> While both of these can be normal age-related eye conditions, the ipsilateral nature and timing of both cutaneous and ophthalmic findings is a conspicuous association.

PWSs in the V1 distribution can be a strong predictor of neuro-ocular involvement.<sup>12</sup> In our case, the patient's PWS appeared several years before his ophthalmologic findings, and while benign in nature, our patient did state some increasing left-side blurriness. As such, we recommend an ophthalmologic exam for any patient presenting with an acquired PWS involving the V1 or V2 distribution.

Some common entities that could be included in the differential diagnosis of PWS include various forms of hemangiomas (e.g., glomeruloid hemangiomas), tufted angiomas and Kaposi sarcoma. Other considerations for differential, workup and treatment are based on previously published case reports. Notably, Pickert et al. described morphea that mimicked an acquired port wine stain.<sup>13</sup> The correct diagnosis was made after several PDL laser treatments. As such, the importance of cutaneous biopsy cannot be underestimated before such treatments in a lesion with questionable clinical appearance or given history. In our particular case, biopsy was performed to rule out angiosarcoma, which has a 2:1 male predilection, most commonly appears in the seventh decade and has a preference for the head and neck region.<sup>14</sup>

A more recent study by Parsa et al. has suggested that PWSs are due to intracranial circulation abnormalities and may result in cutaneous findings, implying that SWS is a product of "acquired venous obstruction rather than neural dysfunction."<sup>15</sup> Other studies suggest abnormalities in blood vessel connective tissue and associated nerve supply.<sup>16-17</sup> Histopathological evidence supports the neural mechanism theory of venous ectasia as documented by decreased nerve density within cutaneous biopsy specimens.<sup>18</sup> Considering the aforementioned, it is plausible to say that acquired PWS may be due to an occlusive event in the cutaneous vasculature, whether traumatic or thrombotic in nature, and that the precise etiology on a molecular level may be neural or strictly vascular.

Genetic studies have indicated the presence of a GNAQ somatic activating gene mutation that encodes p.Arg183Gln amino acid substitutions in skin and brain tissue from patients with Sturge-Weber syndrome as well as those with non-syndromic PWS.<sup>19</sup> The gene makes a Gq protein whose cell surface receptors, when activated by ligand, bind and hydrolyze GTP. This initiates an intracellular MAPK signaling cascade. The mutation locks Gq into a mildly activated state. This supports the long-standing hypothesis that SWS and acquired port wine stains are caused by the same underlying somatic mutation dependent on when and where in development

the somatic mutation occurs<sup>20-21</sup>. Given this genetic activating mutation, it can be postulated that the venodilatation observed in port wine stains is due to the increased GTP, which leads to smooth muscle relaxation in walls of post-capillary venules.

## Conclusion

Acquired PWSs are much less common than their congenital counterparts. While not catalogued or classified as being part of any syndromic condition, their presence near the eye or in the V1 or V2 distribution warrants an ophthalmology workup to rule out any associated malignant or other potentially serious sequelae. PWSs, whether acquired or congenital, may respond well to PDL laser therapy. Our patient was fortunate to respond well after only two treatments, as facial and distal-limb PWSs can be more resistant to laser therapy. Other treatment modalities include embolization or skin grafting, but these options require an extensive multi-disciplinary approach.

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**Correspondence:** J. Hibler, DO;  
drjhibler@yahoo.com

# Common Non-Pharmacologic Interventions in the Prevention of Pediatric Atopic Dermatitis

Karsten Johnson, DO,\* Collin M. Blattner, DO,\*\* John Young III, MD\*\*\*

\*Traditional Rotating Intern, PGY-1, Good Samaritan Regional Medical Center, Corvallis, OR

\*\*Traditional Rotating Intern, PGY-1, Good Samaritan Regional Medical Center, Corvallis, OR

\*\*\*Director, Dermatology Residency Program, Silver Falls Dermatology, Salem, OR

## Abstract

*As the incidence of pediatric atopic dermatitis (AD) continues to increase, dermatologists may find themselves talking to concerned parents about strategies for disease prevention. In this article, we present the current evidence for options that may help decrease a child's risk of developing AD. Specifically, we address whether maternal antigen avoidance, probiotic supplementation, vitamin D supplementation, and emollients are effective in preventing AD in the pediatric population.*

## Introduction

Atopic dermatitis is a chronic disease that affects more than 20% of children and may continue into adulthood.<sup>1</sup> If persistent, the disease may cause significant irritation in daily life, financial burden, and social stigmatization. There is no cure for atopic dermatitis, and current therapies only provide symptomatic relief. Although the cause of atopy is not completely understood, it has a multifactorial etiology. The environment, barrier dysfunction, genetics, and an altered pro-inflammatory immune response have all been implicated. Despite the best efforts of dermatologists, the prevalence of atopic dermatitis in the developed world has risen over the last few decades.<sup>1</sup> This problem has led countless parents to seek the advice of dermatologists in an effort to prevent the development of atopy in their child.

Common questions that dermatologists encounter from parents with a family history of severe atopy or from mothers breast-feeding infants with AD are whether maternal antigen avoidance, probiotic supplementation, vitamin D supplementation, or emollients can reduce the risk of developing this disease. Parents also ask if AD is associated with their child developing behavioral disorders such as attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD).<sup>2</sup>

Because of the substantial increase in pediatric atopic dermatitis (AD) cases over the last three decades, there is a necessity to determine if any preventative measure can reduce the incidence of disease. This editorial briefly summarizes the best available evidence to assist busy dermatologists in providing practical, cost-effective solutions for parents who want to decrease their child's risk of developing AD.

## Evidence of Prevention

### Antigen Avoidance

Expectant mothers should be advised against antigen avoidance. In a 2014 Cochrane review, five trials that included 952 patients found that maternal avoidance of milk, eggs, and other potentially "antigenic" foods during pregnancy, breast-feeding, or both does not prevent childhood AD (Table 1).<sup>3</sup> Of importance, one trial found that women who avoided eating these foods gained significantly less weight during pregnancy

(mean difference -3.00, 95% CI -5.21 to -0.79), which raises the possibility of adverse nutritional effects on the mother or fetus.<sup>4</sup> Further concerns associated with maternal antigen avoidance include a higher (but statistically unstable) risk of preterm birth (RR 10.06, 95% CI 0.53 to 192.26) and a possible adverse effect on mean birthweight (MD -83.45, 95%CI-221.87 to 54.97).<sup>5</sup> Conversely, they should be made aware that a maternal diet that is rich in wheat, dairy products and calcium might reduce the risk of atopy and infantile eczema.<sup>6,7</sup>

### Vitamin D

There is currently insufficient evidence to recommend the use of vitamin D supplementation during pregnancy. Although controversial, one study found that higher maternal intake of vitamin D increased the risk of infantile eczema.<sup>6</sup> This is counterintuitive to the recent association of low levels of vitamin D in the cord blood and AD.<sup>8-9</sup> Furthermore, vitamin D supplementation may have a therapeutic role in the treatment of AD.<sup>10-11</sup> Larger trials over a longer time period with supplementation for both mother and infant are necessary to determine if vitamin D truly has a protective effect against AD.

### ADHD and ASD

Atopy has previously been linked to an increased incidence of attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD). However, the relationship was mostly temporal, and until recently, there were no large longitudinal studies that addressed this claim. The largest study to date involved 14,812 subjects with any atopic disease and 6,944 non-atopic subjects without history of atopy.<sup>2</sup> The subjects were born between 1997 and 2000 and were followed through December 31, 2010. The study concluded that children who developed atopic disease before age 3 had an increased risk of developing ADHD (hazard ratio [HR]: 1.97) and ASD (HR: 3.40) in later life.<sup>2</sup> This finding further substantiates the significance of atopic disease prevention for infants and children.

### Probiotics and Prebiotics

The American Academy of Pediatrics (AAP) last updated its stance on the use of probiotics and prebiotics in November 2010. The AAP

states that, "Although the results of some studies support the prophylactic use of probiotics during pregnancy and lactation and during the first six months of life in infants who are at risk of atopic disorders, further confirmatory evidence is necessary before a recommendation for routine use can be made."<sup>12</sup> Since that time, numerous publications have suggested that probiotics are helpful in the prevention of infantile AD. A 2008 DARE review of 1,429 infants revealed a significant risk reduction for AD after prebiotic supplementation in infants.<sup>13</sup> A 2012 meta-analysis of seven randomized controlled trials (RCTs) revealed a significant risk reduction of AD in 2- to 7-year-old children after prenatal lactobacilli administration.<sup>14</sup> These findings were further supported by a meta-analysis of 16 RCTs in which prenatal and then postnatal probiotic supplementation protected against AD in both normal and high-risk infants.<sup>15</sup>

Only four studies have evaluated the long-term outcomes of using probiotics for the prevention of pediatric AD (up to 9 years of age), and they have yielded mixed results (Table 2). This finding indicates the possibility of a species-specific benefit and a lack of standardization in study design.<sup>15</sup> Three of the four studies found that *Lactobacillus rhamnosus* GG (LbR) consistently reduced the incidence of AD, but despite conflicting study outcomes, a May 2015 meta-analysis concluded that probiotics likely prevent the long-term development of AD.<sup>16</sup> *Lactobacillus rhamnosus* GG transfers from the mother to the child in utero, while other strains cannot.<sup>17</sup> It appears that the strain of bacteria is important when deciding what to recommend to the patient, but further probiotic species-specific studies must be performed before drawing definitive conclusions.

There is strong evidence to support that breast-feeding during the first four months of life causes a reduction in the incidence and severity of atopic disease in patients at high risk (those with a first-degree relative with AD).<sup>18</sup> A meta-analysis of 18 prospective studies and the German Infant Nutritional Intervention studies found decreased AD incidence in high-risk infants who were breast-fed compared to those fed cow's milk formula.<sup>19-21</sup> However, breast-feeding only provides a modest risk reduction

**Table 1. Maternal antigen avoidance trials summarized in Cochrane Review (adapted from Kramer et al.<sup>3</sup>)**

Author	Type	Participants	Interventions	Overall Findings
Appelt 2004	Randomized control trial	497 Canadian mothers of infants from high-risk families, defined as having at least 1 first-degree relative with asthma or 2 with a history of other IgE-mediated allergy	<u>Experimental</u> : complete avoidance of peanut, nuts, and fish and decreased intake of milk and eggs during the third trimester of pregnancy and while breastfeeding for up to 1 year. A partially hydrolyzed formula supplement was provided for the first year, if required. <u>Control</u> : usual care and diet.	Trial did not report on atopic eczema or other allergic disease outcomes, but found no evidence of sensitization to milk, egg, or peanut antigen on skin-prick testing at one, two, or seven years of age.
Cant 1986	Randomized crossover trial	19 U.S. mothers of infants 6 weeks to 6 months of age with atopic eczema	<u>Experimental</u> : maternal exclusion of cow milk, egg, chocolate, wheat, nuts, fish, beef, chicken, citrus fruits, colorings, and preservatives, with use of soya-based milk substitute for 4 weeks. <u>Control</u> : same dietary exclusions for same duration (4 weeks), but substitute contained cow milk and egg. Each of the 2 interventions allocated to all subjects in randomized order.	Dietary antigen avoidance by mothers of infants with established atopic eczema was associated with a non-significant reduction in eczema severity.
Falsh-Magnusson 1987	Randomized control trial	212 pregnant Swedish women with positive family history of allergy (herself, husband, or previous children)	<u>Experimental</u> : cow milk and egg avoidance diet from 28 weeks of gestation. <u>Control</u> : normal diet.	Restricted diet during pregnancy was associated with a small but statistically significant lower mean gestational weight gain (mean difference -3.00, 95% CI -5.21 to -0.79) percentage of pre-pregnancy weight (i.e., 1.8 kg for a 60-kg woman).
Lilja 1988	Randomized control trial	171 pregnant women in Stockholm/Uppsala with a history of respiratory allergy to pollen and/or dander.	<u>Experimental</u> : low-milk and low-egg diet during third trimester. <u>Control</u> : high-milk and high-egg diet during third trimester.	Cord blood IgE levels were higher in the experimental (antigen avoidance) group. Longer-term atopic outcomes not reported.
Lovegrove 1994	Randomized control trial	26 pregnant English women with atopic histories in themselves or in partners, recruited at 30 weeks' gestation	<u>Experimental</u> : milk-free diet from 36 weeks' gestation and during lactation. <u>Control</u> : unrestricted diet.	No significant protective effect of maternal antigen avoidance.

of about 33% against AD, and it is important to note that this only applies to children who have a first-degree relative with AD.<sup>18-20</sup> Some studies involving children with no family history of AD suggest that breast-feeding has no effect on the incidence.<sup>20</sup> Another study of 15,430 mother-child pairs suggested an increased risk of AD in children exclusively breast-fed for the first four months who have no family history of allergy.<sup>21</sup> However, the incidence of AD among infants who were exclusively breast-fed was still lower than those who were never breast-fed (11.6% versus 11.8%).<sup>21</sup> There is no formal recommendation from a national organization regarding breast-feeding and AD, but the World

Health Organization recommends that mothers "exclusively breast-feed their child for the first six months of life."<sup>22</sup> More studies are needed to determine the effect of breast-feeding in children with no family history of AD.

#### Emollients

Although the literature is limited, daily application of moisturizer for the prevention of AD in neonates at high risk for AD is perhaps the most exciting positive news to date. One randomized controlled trial (n=118) found that Japanese neonates who received daily moisturizer had a 32% reduced risk of developing AD compared to control subjects (P = .012, log-rank test).<sup>23</sup> Another study (n=124) found that the

daily use of emollients provided a 50% relative risk reduction in the cumulative incidence of AD at 6 months of life (relative risk, 0.50; 95% CI, 0.28-0.9; P = .017).<sup>24</sup> Few studies have compared the clinical effect of specific emollients, but a large review suggests that the most clinical improvement occurred with urea- and glycerin-based emollients.<sup>25</sup> If confirmed in larger trials, the daily use of emollients following birth for infants with a high risk of AD will be a novel, simple, and safe approach to the primary prevention of AD.

#### Conclusion

Maternal antigen avoidance does not prevent

**Table 2. Long-term outcomes of using probiotics for the prevention of pediatric AD**

Author	Number of participants	Age	Dose	Supplementation Timeline & Overall Findings
Kalliomaki et al.	116	7	1 x 10 <sup>10</sup> cfu LBR	From 36 weeks of gestation for mothers and during first 6 months of life for infants. Probiotics prevented pediatric AD and atopic sensitization compared to placebo group (42.6% vs 66.1%; RR, 0.64; 95% CI, 0.45-0.92)
Kuitunen et al.	891	5	Twice daily capsule of 5x10 <sup>9</sup> cfu LBR; 2x10 <sup>8</sup> cfu Bifidobacterium breve; 2x10 <sup>9</sup> cfu Propionibacterium freudenreichii. Infants received same probiotic once daily mixed with 20 drops of syrup containing 0.8 g of galactooligosaccharides	From 36 weeks of gestation for mothers and during first 6 months of life for infants. Probiotics reduced the incidence of atopy in high-risk children delivered by cesarean section but not in total cohort
West et al.	121	8-9	Lactobacillus paracasei 1x10 <sup>8</sup> cfu per serving	No maternal supplementation. Infants supplemented from 4 to 13 months of age with Lactobacillus paracasei added to cereal. No long-term effects for preventing pediatric AD in cohorts who received Lactobacillus paracasei
Wickens et al. (3 trials)	A) n= 474 at 2 years B) n= 425 at 4 years C) n= 310 at 6 years	A) 2 B) 4 C) 6	LBR 6 x 10 <sup>9</sup> cfu/day; Bifidobacterium animalis subsp. lactis 9x10 <sup>9</sup> cfu/day	A) Maternal supplementation from 35 weeks gestation until 6 months if breastfeeding and infant supplementation until 2 years with LBR halved cumulative prevalence of eczema at 2 years in high risk infants compared to placebo (P = .01) (hazard ratio [HR], 0.51; 95% CI, 0.30-0.85) B) LBR supplementation stopped at 2 years, and at age 4, cumulative prevalence of eczema was still significantly reduced (HR 0.57 (95% CI 0.39-0.83)) C) Significantly lower cumulative prevalence of eczema at 6 years (HR = 0.56, 95% CI 0.39-0.80) ***Bifidobacterium had no significant effect

AD and may have a harmful effect on the fetus.<sup>3</sup> Vitamin D supplementation may have a role in the treatment of AD, but more trials are needed to evaluate the efficacy of vitamin D as a preventative measure against it.<sup>10-11</sup> Prenatal and postnatal supplementation with probiotics, specifically with *Lactobacillus rhamnosus* GG, has the best evidence of preventing AD and is a relatively inexpensive option.<sup>13-15</sup> Breast-feeding for the first four months of life only has a protective effect against AD if the child is at high-risk.<sup>15-17</sup> Although further studies must be done to confirm early findings, the daily use of urea- or glycerin-based emollients following birth in newborns with a high risk for AD is a simple and cost-effective option for the primary prevention of AD.<sup>23-25</sup>

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**Correspondence:** Collin M. Blattner, DO, 3600 NW Samaritan Dr., Corvallis, OR; [collin.blattner@gmail.com](mailto:collin.blattner@gmail.com)

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# Inflammatory Linear Verrucous Epidermal Nevus (ILVEN) Worsening During Pregnancy: A Case Presentation and Discussion

Felicia E. Ekpo, DO,\* J Ryan Jackson, DO,\* Brianna McDaniel, DO,\*\* Carla D. Rohena, PA-C,\*\*\* Christopher Cook, DO, FAOCD,\*\*\*\* Jonathan S. Crane, DO, FAOCD\*\*\*\*\*

\*Traditional Rotating Intern, Sampson Regional Medical Center, Clinton, NC

\*\*Dermatology Resident, PGY-2, Sampson Regional Medical Center, Clinton, NC

\*\*\*PA-C, DermOne, Clinton, NC

\*\*\*\*Dermatologist and Clinical Instructor, Sampson Regional Medical Center Dermatology Residency, Clinton, NC

\*\*\*\*\*Medical Director, DermOne of NC and VA; Dermatology Co-course Director, Campbell University School of Osteopathic Medicine; Dermatology Residency Director, Sampson Regional Medical Center, Clinton, NC

## Abstract

*Epidermal nevi are congenital hamartomatous lesions that are typically present at birth, though they can occur anytime during childhood and rarely appear in adulthood. Inflammatory linear verrucous epidermal nevus (ILVEN) is a rare variant of epidermal verrucous nevus that is four times more common in females than males.<sup>1</sup> This condition is clinically characterized by the appearance of recurrent inflammatory phenomena, with chronic eczematous and psoriasiform aspects, usually unilateral, with pruritus, and it is often refractory to therapy.<sup>2,3</sup> We report a case of ILVEN syndrome in a 27-year-old female patient who demonstrated very significant clinical worsening during pregnancy.*

## Introduction

Inflammatory linear verrucous epidermal nevus (ILVEN) is a benign cutaneous hamartoma that consists of erythematous, pruritic, inflammatory plaques that occur as a linear band along a line of Blaschko. ILVEN is a chronic condition, thus patients typically seek medical attention for relief of discomfort along with cosmetic concerns. A few reported therapeutic approaches include topical agents, dermabrasion, cryotherapy, laser therapy and excision. However, no one treatment has been consistently successful. Therapy is often unsatisfactory.<sup>4</sup>

We report a case of ILVEN in a 27-year-old female patient who demonstrated very significant worsening, determined by an increase in thickness from approximately 1 mm to 7 mm, during her second trimester of pregnancy. The average thickness of ILVEN is 1 mm to 3 mm.<sup>5</sup> In our literature search of ILVEN in pregnancy, we found no other cases reporting marked worsening of ILVEN during pregnancy.

## Case Report

A 25-year-old African American female, currently in her second trimester of pregnancy, presented with history of a pruritic scaly eruption on the right lower extremity. The lesions first appeared at the age of 5 and gradually progressed in size, with significantly accelerated rates of growth during pregnancy. Aggravating factors for her included pregnancy and sunlight exposure, which resulted in increased pruritus and crusting. Her past medical history was significant for scalp psoriasis, which was managed with shampoos containing tar. The patient was otherwise healthy.

Physical examination revealed a hyperkeratotic linear plaque overlying a base of friable erythema. This extended from the right posterior ankle to the popliteal fossa (**Figure 1**). The anterior right leg showed linear-to-ovoid pink patches with areas of central crusting (**Figure 2**).

## Microscopic Findings

Our patient had multiple biopsies in the past consistent with ILVEN. We performed a skin

biopsy of the right calf (**Figures 3a, 3b**), which demonstrated marked psoriasiform epidermal hyperplasia with slight papillomatosis. There were areas of alternating orthokeratosis with a thickened granular layer, and parakeratosis with loss of the granular layer. Collections of neutrophils with scale and crust were seen in the cornified layers of the epidermis. PAS stain was negative for fungi. The psoriasiform process resembled some changes seen in psoriasis, but the histopathological findings were more consistent with ILVEN. Clinically, the lesion had been present for 22 years, confirming the diagnosis of ILVEN.

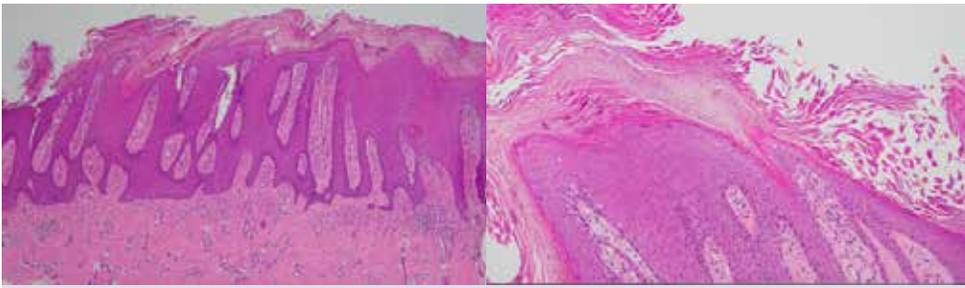
Our patient did not see improvement with trials of clobetasol ointment, topical calcipotriene, entanercept, adalimumab, methotrexate, or betamethasone/calcipotriene prior to her pregnancy. Topical gentamicin 1% ointment was prescribed for potential secondary infection. Application of the ointment three times per day did not result in significant clinical improvement but was successful in eliminating the patient's pruritus.



Figure 1. Hyperkeratotic papules coalescing into a large, linear plaque overlying a base of friable erythema extending from the right posterior ankle to the popliteal fossa (pre-pregnancy, Jan. 2014).



Figure 2. Brown verrucous papules coalescing into a linear plaque with overlying crust on a base of erythema on the right leg. Worsening of ILVEN with increase in overlying crust at 25 weeks pregnant (Sept. 2015).



Figures 3a, 3b. Histopathology from right calf skin biopsy showing psoriasiform epidermal hyperplasia, alternating orthokeratosis with a thickened granular layer, and parakeratosis with loss of the granular layer.

## Discussion

ILVEN is a rare form of epidermal nevus caused by somatic mutations, reflecting genetic mosaicism, though the exact physiopathology remains uncertain.<sup>4</sup> It may be associated with an increase in the production of interleukin 1 and interleukin 6, along with tumor necrosis factor- $\alpha$  and intercellular adhesion molecule 1.<sup>6</sup> ILVEN is more common among females and children and is sometimes familial.<sup>7</sup>

Altman and Mehregan established the classic ILVEN diagnostic criteria in 1971.<sup>8</sup> Morag and Metzker modified the criteria in 1985 to include unilateral, linear verrucous eruption (most frequently involving the left leg), severe pruritus, early age of onset, and resistance to therapy.<sup>1,3</sup>

Prior research has shown that ILVEN is often resistant to topical steroids, 5-fluorouracil cream, tretinoin cream, podophyllin ointment and tar preparations.<sup>9</sup> The variability and inconsistency of medical management makes successfully treating this syndrome difficult and temporary. Surgical excision is not recommended due to extensive scarring and frequent relapse of disease.<sup>10</sup> Literature has shown some successful outcomes using CO<sub>2</sub> therapy.<sup>11</sup> However, no research has demonstrated consistent results supporting the superiority of any specific therapy.<sup>2</sup>

ILVEN has been associated with other disorders, including autoimmune thyroiditis, lichen amyloidosis, HIV-1 infection, and skeletal defects.<sup>12-15</sup> ILVEN is also associated with ocular and oral defects. Some of the ocular defects include astigmatism, choristomas, colobomas of the eyelid, iris, choroid and retina, and cortical blindness.<sup>16</sup> Oral involvement is rare, but if involved, the lips, tongue and palate are most frequently affected with wart-like, condylomatous, mammilated, or verrucous plaques ranging in color from normal oral mucosa to yellow, white, tan, dark brown, or gray.<sup>17</sup>

ILVEN should be considered in the differential diagnosis if the patient presents with extensive verrucous, pruritic epidermal nevi, and/or systemic abnormalities. With the diffuse array of associations ILVEN may have, a thorough mucocutaneous, neurologic, ophthalmic, and orthopedic examination is appropriate. Regular follow-up is encouraged due to the 15% to 20% risk of malignant transformation and potential development of systemic manifestations, which is

estimated to occur in one-third of patients with ILVEN.<sup>18,19</sup>

## Conclusion

ILVEN is markedly resistant to therapy. ILVEN has previously been treated with topical glucocorticoids applied under occlusion, intralesional corticosteroids, tretinoin 0.1% and fluorouracil 5%, anthralin, tar vitamin D3 analogues, surgical excision, cryotherapy and laser therapy. No research has demonstrated consistent results as to the superiority of any one of these therapies.<sup>3</sup> Treatment is further limited in patients with ILVEN during pregnancy. We hypothesize the clinical worsening of ILVEN in our patient during her second trimester of pregnancy is due to an imbalance of hormone ratios. Studies suggest the increase in sex hormones during pregnancy, a natural state of immunomodulation, may play a potential role in the exacerbation of various inflammatory dermatological diseases.<sup>20,21</sup>

Our patient declined further treatment until after her pregnancy. Due to unsuccessful therapies in the past, laser ablation will be the next treatment modality. Resurfacing lasers, such as Er:YAG and CO<sub>2</sub> lasers, have proven to be effective at decreasing the thickness of ILVEN. Er:YAG laser treatment has been successful in the treatment of superficial, discrete ILVEN lesions.<sup>22</sup> Recent CO<sub>2</sub> laser clinical trials have demonstrated greater than 50% reduction in 50% of ILVEN patients treated with CO<sub>2</sub> laser ablation, and greater than 75% reduction in 30%. Minor adverse effects consisted of scarring and hyperpigmentation, which was seen in 20% and 25%, respectively.<sup>5</sup>

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**Correspondence:** Brianna McDaniel, DO;  
Sampson Regional Medical Center, Clinton, NC;  
mcdaniel.brianna@gmail.com

# Anterior Cervical Hypertrichosis: A Case Report and Review of the Literature

Bridget E. McIlwee DO,\* Patrick J. Keehan, DO,\*\*

\*Dermatology Resident, OGME-3, University of North Texas Health Science Center/TCOM, Fort Worth, TX

\*\*Faculty, Dermatology Residency, University of North Texas Health Science Center/TCOM, Fort Worth, TX; Clinical Director and Dermatologist, Premier Dermatology, Fort Worth, TX

## Abstract

*Anterior cervical hypertrichosis (ACH) is a rare form of localized hypertrichosis. It typically arises sporadically and is often an isolated finding. However, familial cases of ACH have been reported in association with other aberrations including skeletal abnormalities, sensory and motor neuropathies, mental retardation, and developmental delay. We present the case of a 5-year-old female with ACH in the absence of any family history of localized hypertrichosis and without any other mental or physical abnormalities.*

## Introduction

Unlike hirsutism, which is an excess growth of terminal hair in androgen-dependent areas such as the face, chest, or back, hypertrichosis is an increased density of hair growth in body areas that are not androgen-dependent. Hypertrichosis may occur in generalized or localized forms.<sup>1</sup> Here, we discuss a localized form of the condition known as anterior cervical hypertrichosis, or ACH. Though localized hypertrichoses may occur sporadically and in isolation, some forms have been reported in association with significant skeletal and neurologic abnormalities. Given the potential for morbidity, a diagnosis of ACH or any other form of localized hypertrichosis warrants a complete physical exam and additional studies as indicated to rule out associated neurological and skeletal abnormalities.

## Case Report

A 5-year-old white female presented to the clinic as a new patient with complaints of hair growth. Her parents noted that at approximately 3 years of age, the patient began to grow a patch of hair on the anterior neck. The hair was light brown in color and had not changed in appearance since they first noticed it. However, the hair continued to grow longer. The parents had not pursued any treatment other than trimming the hair regularly.

The patient did have eczema, but her health history was otherwise unremarkable. There was no family history of unusual or localized hair growth. There was no family history of neuropathies, skeletal abnormalities, or learning disabilities.

On physical exam, the patient had a 1.5 cm patch of light brown, terminal hair growing on the anterior neck, superior to the laryngeal prominence (**Figures 1, 2**). There was no nevus or pigment underlying the patch of hair. There were no other patches of ectopic hair growth noted on thorough physical exam. Aside from a banal eczematous plaque on the right posterior knee, the remainder of her examination – including gross skeletal, motor and sensory exams – was unremarkable. We therefore diagnosed her with anterior cervical hypertrichosis.

## Discussion

Forms of localized hypertrichosis may occur congenitally or as acquired conditions. Acquired forms of localized hypertrichosis have been reported to arise after topical medications, such as corticosteroids, androgenic hormones, methoxsalen, diphenylhydantoin, and minoxidil.<sup>2,3</sup> Localized hypertrichosis may also arise in the settings of local trauma, cutaneous hyperemia, peripheral neuropathy, chronic inflammation, or pretibial myxedema.<sup>4</sup> Localized hypertrichosis most commonly occurs in the sacral area (“fawn tail”), but it may also occur in lumbar, thoracic, or cervical areas along posterior midline.<sup>5,6</sup> More rarely, anterior midline cases of localized hypertrichosis have been reported. Cases of localized hypertrichosis have also been reported on the palms, soles, and elbows.<sup>7-11</sup>

Especially when these areas of localized hypertrichosis are found along the posterior midline, they are often associated with underlying defects such as spina bifida, meningocele, scoliosis, or other bony or neurologic malformations. When localized hypertrichosis is associated with underlying skeletal or neurologic abnormalities, many can be surgically corrected; and some, like diastematomyelia, can cause permanent functional damage if not corrected with due haste.<sup>12</sup> When localized hypertrichosis occurs in an anterior distribution, it has most commonly been associated with generalized neuropathy,

though other systemic associations and rare cases of underlying anterior bony deformities have also been reported.<sup>4</sup> Both anterior and posterior localized hypertrichosis may also occur without other associated conditions.

Anterior cervical hypertrichosis (ACH) – also called ‘hairy throat’ – is a form of hypertrichosis in which there is terminal-hair growth on the anterior midline neck, superior to the laryngeal prominence. ACH may occur in a familial or sporadic fashion. There have been several reported cases of familial anterior cervical hypertrichosis.<sup>4,5,13,14</sup> In one case report of a consanguineous family with three members affected by anterior cervical hypertrichosis, all three individuals also had peripheral sensory neuropathy and bilateral hallux varus, two had subclinical motor neuropathy, and one had optic nerve atrophy as well as macular degeneration.<sup>15</sup> These associated conditions would suggest an autosomal-recessive pattern of inheritance. However, another case report of anterior cervical hypertrichosis discussed a family in which there were seven affected members, comprising three generations. The only other health problem found within the family was Turner syndrome, which would seem to suggest an autosomal-dominant pattern of inheritance.<sup>14</sup> In yet another case report of familial anterior cervical hypertrichosis, three family members were affected. One of the family members had mild myopia, while the other two had no other medical problems. There

Figure 1



Figure 2



was no consanguinity within the family.<sup>14</sup>

Sporadic cases of anterior cervical hypertrichosis have also been reported.<sup>6,16,17</sup> In cases of sporadic anterior cervical hypertrichosis, the majority of patients reported have had no other associated anomalies or medical conditions.<sup>6,17</sup> However, some sporadic cases of ACH have been reported in association with diffuse weakness and developmental delay;<sup>16</sup> posterior hypertrichosis, moderate mental retardation, abnormal EEG, microcephaly, and hallux varus;<sup>18</sup> and posterior hypertrichosis, moderate mental retardation, dysmorphic facies, and hyperopia.<sup>19</sup>

In early 2015, Megna et al. assessed the 40 cases of ACH that have been published to date. Twenty-seven of the published cases were familial (67.5%), and 13 were sporadic (32.5%). Literature review reveals that females are more often affected with ACH than males (75% of reported cases). In the vast majority of cases, ACH presents as a solitary defect (77.5% of reported cases). In the 22.5% of reported cases in which ACH was associated with other abnormalities, the most common were peripheral sensory and motor neuropathy (55% of cases) followed by mental retardation (22%) and developmental delay (22%).<sup>20</sup>

Four out of seven reported cases (57%) of familial ACH have been associated with other systemic abnormalities. Three of 10 cases (30%) of sporadic ACH have had other associated systemic abnormalities.<sup>20-26</sup>

Because of the potential for ACH to be associated with other systemic abnormalities, complete neurologic and ophthalmologic assessments are warranted in all patients presenting with findings of ACH.<sup>21</sup> If warranted based on history or physical exam, other diagnostic studies may include skeletal survey (to rule out spina bifida or abnormalities of the foot) or blood work to assess karyotype and rule out endocrine abnormalities.<sup>20</sup>

In three out of seven reported cases of familial anterior cervical hypertrichosis, affected family members have been both male and female. Most sporadic cases of ACH have involved only females, although one reported case included two males and one female.<sup>14</sup> The pattern of inheritance of ACH has not yet been elucidated, though the pedigrees of some families with ACH seem to suggest either an autosomal-dominant or an X-linked dominant pattern.<sup>13,14,16-18</sup> In cases of ACH associated with neuropathy, inheritance appears to be autosomal-recessive.<sup>4,17,22,23</sup>

Despite postulations regarding the mode of inheritance of ACH, the etiology of the disorder remains unknown. In contrast to lumbar hypertrichosis, in which the localized increased hair density may signal an underlying skeletal abnormality (spina bifida), ACH has yet to be reported in association with defects of underlying structures. Therefore, it is unlikely that ACH arises as a secondary effect of underlying skeletal or other abnormalities.<sup>19</sup> Furthermore, in contrast to generalized hypertrichoses (e.g., Ambras syndrome), which some have suggested to be an atavism, ACH and other localized

forms of hypertrichosis seem more compatible with a homeotic gene alteration resulting in ectopic terminal-hair growth.<sup>27,28</sup> However, this phenotypic change has not been substantiated in mouse models of Hox gene alterations.<sup>19</sup>

In the absence of associated abnormalities, ACH is primarily of cosmetic concern to the patients and their families. Treatments are those commonly utilized to treat unwanted hair on other areas of the body, including trimming, waxing, bleaching, electrolysis, and IPL.<sup>2,24</sup>

## Conclusion

It is thought that ACH is vastly underreported. Our report represents a sporadic case of ACH in a patient without any other systemic disorders, but we wish to publish it to raise awareness of ACH and its most common associations, some of which are serious and may be treated effectively if recognized promptly.

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**Correspondence:** Bridget E. McIlwee, DO,  
University of North Texas Health Science  
Center, 855 Montgomery Street, 5th Floor,  
Fort Worth, TX 76107; Ph: 817-735-2922;  
F: 817-735-5022; bridget.mcilwee@unthsc.edu

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# DRESS Syndrome: Improvement of Acute Kidney Injury and Rash with Corticosteroids

Dawnielle Endly, DO,\* Jonathan Alterie, BS,\*\* David Esguerra, DO,\*\*\* Richard A. Miller, DO\*\*\*\*

\*Co-lead Author, Dermatology Resident, Nova Southeastern University College of Osteopathic Medicine/Largo Medical Center, Largo, FL

\*\*Co-lead Author, 4th-year Medical Student, Chicago College of Osteopathic Medicine, Chicago, IL

\*\*\*Clinical Professor, Nova Southeastern University College of Osteopathic Medicine, Largo, FL

\*\*\*\*Program Director, Dermatology Residency Program, Nova Southeastern University College of Osteopathic Medicine/Largo Medical Center, Largo, FL

## Abstract

*DRESS syndrome (drug rash with eosinophilia and systemic symptoms) is a rare and potentially life-threatening idiosyncratic drug reaction that may involve a number of visceral organs. This syndrome often mimics other serious systemic disease processes, making the diagnosis complicated and often delayed. Herein, we present a unique case of DRESS syndrome accompanied by acute interstitial nephritis that responded to oral prednisone during a hospital stay.*

## Introduction

DRESS syndrome is a drug reaction that usually manifests with fever, a pruritic macular and papular rash, hematologic abnormalities (leukocytosis, eosinophilia, and/or atypical lymphocytes), and internal organ involvement. This drug reaction is characterized by a delayed onset, typically occurring two to eight weeks after exposure to the inciting medication.<sup>1</sup> Despite the existence of a scoring system known as RegiSCAR to aid in accurate and prompt diagnosis, the variability in the clinical course and dermatologic manifestations often results in delays.<sup>2</sup>

## Case Report

A 68-year-old female with history of type 2 diabetes mellitus, systolic heart failure with an ejection fraction (EF) of 25%, and Charcot-Marie-Tooth disease presented to the emergency department with progressive leg swelling and a diffuse, itchy rash of about two months' duration. The rash began on the left flank and face approximately four weeks after starting furosemide for fluid overload. No other new medications were initiated or modified in the prior six months. She denied fevers, joint pain, or facial swelling associated with the rash.

She was evaluated by an outside provider one week prior to hospitalization and was prescribed a mid-potency topical steroid cream to be applied twice a day to the most pruritic areas. A biopsy was obtained at that time, revealing sparse perivascular lymphohistiocytic infiltrate with frequent neutrophils and eosinophils in the

superficial dermis. The patient reported minimal symptomatic relief, but the rash progressed and became generalized with total body involvement. Due to clinical suspicion for a cutaneous drug reaction, her primary care provider stopped the furosemide and prescribed spironolactone a few days prior to her hospitalization.

Upon admission, vital signs were all normal. Cutaneous examination revealed diffuse erythematous and violaceous macules and papules with fine white scale and several linear erosions with serosanguinous crusts (**Figures 1-3**). Both lower extremities had 2+ pitting edema up to the hips. No obvious facial edema, vesicles or bullae, or oral mucosal lesions were identified during hospitalization.

Initial laboratory results revealed various abnormalities. A complete blood count demonstrated an eosinophilia of 23% (normal 0-5%) and presence of atypical lymphocytes. A complete metabolic panel revealed many elevated components including: aspartate transaminase (AST) of 102 U/L (15-37 U/L), alanine transaminase (ALT) of 125 U/L (13-61 U/L), alkaline phosphatase of 263 U/L (45-117 U/L), blood urea nitrogen (BUN) of 65 mg/dL (7-18 mg/dL), and creatinine of 1.9 mg/dL (0.6-1.3 mg/dL) compared to her baseline creatinine of 1.0 mg/dL. Urinalysis was positive for leukocyte esterase, red blood cells 2-5/hpf (0-1/hpf), and white blood cells of 10-15/hpf (0-1/hpf). Urine eosinophils were also found to be positive. A urine culture eventually grew *Escherichia coli*, and she was treated for a urinary tract infection. Anti-nuclear antibody, blood cultures, a hepatitis panel, and rapid plasma regain (RPR) were all

negative. An echocardiogram revealed a decrease in EF from 25% at baseline to 10% to 20% with severe diffuse hypokinesia and severe biatrial enlargement. All clinical data was entered into the RegiSCAR group diagnosis chart for DRESS syndrome and revealed a total of 7 (see **Table 1**), confirming a diagnosis of DRESS syndrome.

Given multiple co-morbidities including uncontrolled diabetes, topical treatment with a high-potency topical steroid was initially favored. The possible causative medication, furosemide, had already been stopped prior to hospital admission. An echocardiogram revealed a decrease in ejection fraction to 15% to 20% with severe diffuse hypokinesia and severe biatrial enlargement. Her renal function continued to decline throughout her hospitalization, and given the multitude of possible etiologies (pre-renal from diuretics or heart failure exacerbation, possible interstitial nephritis secondary to DRESS syndrome), nephrology recommended a renal biopsy to aid in definitive diagnosis. On day four of her hospitalization, a renal biopsy was planned, but the patient became anxious and severely hypotensive while on the operating table. Unfortunately, the renal biopsy was not completed, and she required admission to the intensive care unit and vasopressors for several days while her renal function continued to decline.

The patient refused hemodialysis, but agreed to systemic steroids as treatment for possible interstitial nephritis secondary to DRESS syndrome. The patient initially received two intravenous doses of methylprednisolone 125 mg. She was then placed on an oral prednisone



**Table 1. RegiSCAR score for DRESS syndrome<sup>11</sup>**

< 2 = no case, 2-3 = possible case, 4-5 = probable case, > 5 = definite case				Current Case
Features	No	Yes	Unknown	
Fever ( $\geq 38.5^{\circ}\text{C}$ )	-1	0	-1	-1
Enlarged lymph nodes ( $\geq 2$ sites, $\geq 1$ cm)	0	1	0	0
Atypical lymphocytes	0	1	0	1
Eosinophilia	0		0	
700-1,499 or 10%-19.9%		1		
1,500 or $\geq 20\%$		2		2
Skin rash	0		0	
Extent > 50%	0	1	0	1
At least 2 of: edema, infiltration, purpura, scaling	-1	1	0	1
Biopsy suggesting DRESS	-1	0	0	0
Internal organ involvement	0		0	
1		1		
2 or more		2		2
Resolution in more than 15 days	-1	0	-1	0
Rule out $\geq 3$ other potential causes (ANA, blood cultures, hepatitis panel, RPR, chlamydia, etc.)	0	1	0	1
Final Score				7

taper, and within a couple of days her BUN and creatinine began to decline and urine output began to increase. Additionally, there was substantial improvement in the patient's rash and pruritus. After a couple of days, the patient was taken off of vasopressors and determined to be stable for transfer back to the general medicine floor. She was ultimately discharged to a rehabilitation facility on a four-week prednisone taper.

## Discussion

DRESS syndrome, or drug rash with eosinophilia and systemic symptoms, is an uncommon drug reaction that classically has a delayed onset within two to eight weeks after starting the causative medication.<sup>1,3</sup> Incidence of this syndrome ranges from 1 in 1,000 to 1 in 10,000 drug exposures, with a mortality of 10%.<sup>3,4</sup> Two studies noted a predilection for females, with a male-to-female ratio of 0.8:1.0.<sup>2,5</sup>

DRESS syndrome was first attributed to aromatic anti-epileptic medications dating as far back as the 1920s, and it was thus referred to as anticonvulsant hypersensitivity syndrome. A case reported in 1950 describes a classic patient who presented with fever, an exfoliative rash, and jaundice while taking phenytoin.<sup>6</sup> Another notable, early encounter that highlighted this often challenging diagnosis described a patient with lymphadenopathy,

arthralgias, fever, and a pruritic rash mimicking malignant lymphoma while on carbamazepine.<sup>7</sup>

While anticonvulsants remain the most frequently associated drug class, more and more different medications, such as sulfonamides, minocycline, allopurinol, ampicillin, and dapsone, are being deemed likely culprits. For this reason, the former nomenclature, anticonvulsant hypersensitivity syndrome, has fallen out of favor. In one study reviewing 201 potential cases of DRESS syndrome, aromatic anti-epileptic drugs were responsible for nearly 35% of cases.<sup>2</sup> Also significant were the 12% of cases reported to have sulfonamides, particularly dapsone and sulfasalazine, as a possible cause.<sup>2</sup> Despite sulfonamides being commonly suspect, our review of the literature revealed no reports of DRESS syndrome associated with furosemide, a non-antibiotic sulfonamide, prior to this case. Other, less frequently noted culprits are various antimicrobials, antivirals, antidepressants, antihypertensives, NSAIDs and biologic medications.<sup>3,8</sup> While rarely reported to cause DRESS syndrome, minocycline is one antimicrobial worthy of highlighting, particularly for dermatologists. Of note, several studies report minocycline-induced DRESS syndrome occurs primarily in patients with darker skin types (Fitzpatrick V and VI).<sup>9,10</sup> Maubec et al. proposes

the higher melanin content in darker pigmented skin may form a melanin-minocycline complex resulting in accumulation of the causative drug.<sup>10</sup> It would be prudent for dermatologists to consider alternative therapies, perhaps doxycycline, in this specific patient population to help avoid DRESS syndrome and the potentially life-threatening sequelae that may result.

The most common skin finding reported in DRESS syndrome is a morbilliform or mixed macular and papular type of eruption. Exfoliative dermatitis following a diffuse erythroderma, facial swelling, mucosal involvement, and vesicles have also been reported in a number of studies.<sup>1,2,4</sup> Cacoub et al. found 97% of those suffering from DRESS syndrome in their study actually had a rash.<sup>3</sup> More specifically, 60% exhibited a macular and papular rash, 54% had a generalized erythematous rash, and 39% had facial edema.

In addition to the cutaneous manifestations, internal organ involvement is another variable entity in DRESS syndrome. According to Husain et al., the most commonly affected visceral organ is the liver.<sup>4</sup> They found nearly 70% of patients with DRESS syndrome to have abnormal liver function tests. The renal system is less commonly involved. Effects on the kidney can lead to hematuria, proteinuria and elevated BUN and creatinine. The appearance of eosinophils in the

**Table 2. Visceral organs most commonly affected by DRESS<sup>2</sup>**

Organ	Rate
Liver	75%
Kidney	37%
Lung	32%
Spleen	15%
Heart/Musculoskeletal	13%
Pancreas	4%

**Table 3. RegiSCAR inclusion criteria\* for DRESS syndrome<sup>12</sup>**

Hospitalization+
Reaction suspected to be drug-related+
Acute skin rash+
Fever above 38°C
Enlarged lymph nodes in at least two sites
Involvement of at least one internal organ+
Lymphocytes above or below the laboratory limits
Eosinophilia+
Thrombocytopenia

\*At least 3 required for diagnosis  
+Inclusion criteria in current case

urine, as seen in this case, may be an indicator of interstitial nephritis. Though rare, the need for short-term hemodialysis has been documented. Other potentially affected systems are lymphatic, hematologic, pulmonary and cardiovascular.<sup>2,4,8,11</sup> See **Table 2** for a list of the most commonly affected visceral organs in DRESS syndrome.

Due to the variability in presentation, relatively late onset, and long duration even after stopping the causative drug, DRESS syndrome is often a complex, delayed diagnosis. It is important that clinicians first exclude other clinically similar conditions such as lymphoproliferative diseases and autoimmune or infectious diseases. When considering DRESS syndrome, the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria aid in solidifying a diagnosis when confronted with these clinically challenging cases (**Table 1**).<sup>12</sup> Additionally, RegiSCAR requires three or more of the following major criteria for a solid diagnosis of DRESS syndrome: an acute rash, fever above 38°C, lymphadenopathy of at least two sites, involvement of at least one internal organ, platelets below normal laboratory limits, lymphocytes above or below the laboratory limits and/or increased eosinophil counts (**Table 3**). Additional criteria to consider, though not necessarily required for a diagnosis of DRESS syndrome, include hospitalization and/or a suspected drug-related etiology.<sup>12</sup>

Once DRESS syndrome is suspected, discontinuation of the offending agent is the first step in treatment.<sup>1,8</sup> According to Husain et al.,

the decision to begin systemic corticosteroids is dependent upon the overall clinical picture and whether there are signs of visceral involvement.<sup>8</sup> In the absence of internal organ involvement or when transaminase levels do not exceed five times normal, patients may be treated conservatively with topical corticosteroids. In addition, treatment may include H1-antihistamines and emollients for symptomatic relief if pruritus is present. In the presence of visceral involvement and/or elevated transaminase levels greater than five times normal, 1 mg/kg/day of prednisone with a taper regimen over three to six months is warranted. In the case that no improvement is noted with oral prednisone, a three-day course of 30 mg/kg of methylprednisolone intravenously may be administered as pulse therapy.<sup>8</sup>

Even with cessation of the causative medication, mortality is reported to be around 10%.<sup>12,13</sup> However, just as there is variability in DRESS syndrome's clinical presentation, the mortality varies according to the patient's comorbidities, presence or absence of visceral involvement, and amount of time from disease onset to diagnosis and treatment.

## Conclusion

As evident in this particular case, DRESS syndrome is a challenging diagnosis of exclusion that has the potential to progress to a life-threatening illness warranting the use of systemic corticosteroids. The clinical picture is often broad and non-specific, requiring a detailed history. It is important to note the temporal evolution of signs and symptoms, use sound physical exam skills, and closely interpret laboratory values to make the diagnosis of DRESS syndrome. The culprit medication should be discontinued as soon as possible, and the decision to treat with topical or systemic corticosteroids must be based on clinical severity.

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**Correspondence:** Dawnielle Endly, DO; Dawnielleendly@hotmail.com

# Hailey-Hailey Disease Masquerading as Intertriginous Candidiasis for 10 Years

Miguel Villacorta, DO, MPH,\* Brittany P. Smirnov, DO,\*\* Jennifer Moscoso Conde, DO,\*\* Carlos H. Nousari, MD\*\*\*

\*Traditional Rotating Intern, PGY-1, Broward General Medical Center, Fort Lauderdale, FL

\*\*Dermatology Resident, PGY-3, Broward General Medical Center, Fort Lauderdale, FL

\*\*\*Program Director, Dermatology Residency Program, Broward General Medical Center, Fort Lauderdale, FL

## Abstract

*Hailey-Hailey disease (HHD) is a rare, autosomal-dominant genodermatosis that presents as erosive erythematous plaques commonly present with crusting, maceration and fissures in intertriginous locations. HHD may be difficult to distinguish from other intertriginous diseases. Additionally, bacterial or fungal infection can be superimposed on the affected areas, convoluting diagnosis and complicating management of the disease. Making a correct diagnosis and individualizing treatments are important to decrease patient morbidity and reduce complications.*

*We present a patient with HHD that was misdiagnosed as intertriginous candidiasis for 10 years. The proper diagnosis was made after a thorough history was taken and a biopsy was performed. Clinical differences between diseases and common treatment modalities are discussed as well. We highlight the new treatment modalities to improve physician awareness of available interventions.*

## Introduction

In 1939, the Hailey brothers were the first to describe Hailey-Hailey disease (HHD), or benign familial pemphigus.<sup>1</sup> Diagnosis of HHD can prove difficult, as it can present similarly to other intertriginous diseases and with a superimposed infection. It is important for a clinician to be able to distinguish HHD from other intertriginous diseases. Herein, we describe a case of HHD that had been misdiagnosed for 10 years as candidiasis. We focus on differentiating HHD from other diseases and summarize current treatment modalities published in the literature.

## Case Report

A 63-year old Haitian female with a past medical history of hypertension and diabetes presented with complaints of a painful, irritated rash on her posterior neck, bilateral axillary, inframammary,

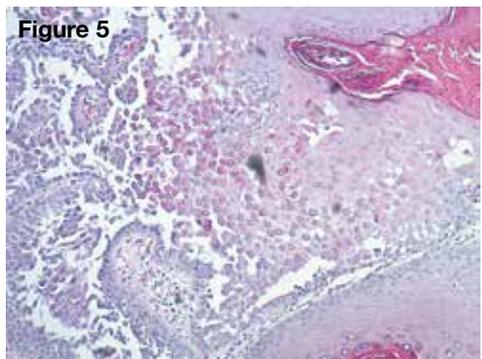
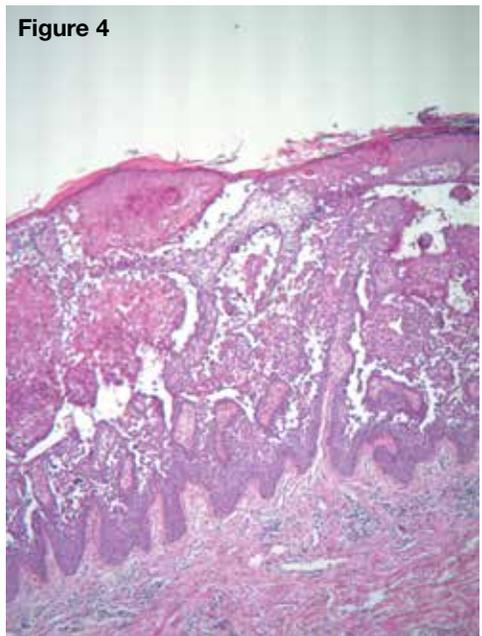
intergluteal and inguinal folds. The patient reported waxing and waning of the eruption for approximately 10 years, occasionally resolving entirely, but eventually recurring. Prior treatments included betamethasone cream to affected areas, as well as oral and topical antibiotics, antifungals, and topical corticosteroids for the treatment of intertrigo and candidiasis. She originally denied a family history of skin disorders or cancers.

Physical examination revealed violaceous-to-brown hyperpigmented plaques with erosions and maceration located on her posterior neck, bilateral axillae, inframammary folds and groin, with scant surrounding satellite macules (Figures 1, 2, 3). Our patient did not exhibit longitudinal leukonychia. Following years of ineffective treatment for intertriginous candidiasis, the patient presented to our clinic, and upon further questioning, reported similar eruptions in three of her sisters, as well as her mother.

Suspecting possible Hailey-Hailey disease, a 4-mm punch biopsy was performed in the left axilla. Histopathologic examination revealed a large focus of acantholytic dyskeratotic cells in a “dilapidated brick wall” pattern, with perinuclear eosinophilia (Figures 4, 5). PAS stain was negative for dermatophytes, and fungal and bacterial cultures performed at the time of biopsy

were positive for only light growth of *Pseudomonas aeruginosa*.

A complete blood count, comprehensive metabolic panel, and lipid panel were ordered in preparation for possible isotretinoin treatment. She was prescribed oral fluconazole and doxycycline in the interim. At the one-month follow up, the patient stated that she noted some improvement with the medical regimen. Nystatin powder and ciprofloxacin were added. Three months later, active areas on the patient’s left axilla and



inframammary folds remained. Clobetasol was added to improve the persistent lesions. Unfortunately, one month later, there was no improvement with clobetasol. At this point the patient had persistent lesions with only some minor improvement in her symptoms. Her prescriptions were adjusted to include fluconazole, tacrolimus, clotrimazole and betamethasone. She returned three months later with improvement in her lesions. The lesions consisted of hyperpigmented patches and mild erythema on her bilateral axilla and inframammary folds without any evidence of maceration. At this point the patient was only using nystatin powder and the topical clotrimazole with betamethasone.

As of her last visit, the patient has been following with our clinic for nine months without any additional flares in her disease. While her blood work for CBC, CMP, and lipid panel returned unremarkable, the patient has not been started on soriatane treatment since she had achieved considerable improvement with her current medical regimen. She was advised to follow up in an additional four months and, if her symptoms worsen, soriatane treatment would be considered.

## Discussion

Hailey-Hailey disease (HHD), also known as benign familial pemphigus, is a rare genodermatosis first described by the Hailey brothers in 1939.<sup>1</sup> The disease is inherited in an autosomal-dominant fashion with complete penetrance but variable phenotypic expression. It can also present as a *de novo* mutation.<sup>2</sup> Affecting males and females equally, HHD typically presents in the second or third decade of life, with an overall estimated incidence of 1 in 50,000.<sup>3,4</sup> The disease is caused by a mutation of the ATP2C1 gene, which encodes the ATP-powered calcium pump protein, hSPCA1, that sequesters calcium into the Golgi apparatus.<sup>5</sup> The impaired calcium pump protein leads to lower calcium levels inside the Golgi apparatus, causing impaired production of calcium-binding transmembrane glycoproteins and subsequent loss of cellular adhesion in the stratum spinosum.<sup>6</sup> Histologically, the acantholysis is classically described as having a “dilapidated brick wall appearance” with the retention of basilar layer adherence to the dermis.<sup>3</sup> Other histologic features include suprabasal decomposition, intraepidermal bullae, epidermal hyperplasia, parakeratosis, and lymphocytic infiltration.<sup>7</sup> Direct immunofluorescence testing is negative.<sup>8</sup>

Hailey-Hailey disease presents as flaccid vesicles or bullae in intertriginous locations such as the axilla, groin, gluteal cleft, and inframammary folds. These fragile vesicles are easily ruptured and are often absent on physical examination. The remaining erosive erythematous plaques commonly present with crusting, maceration and fissures. Patients can experience increases in morbidity as affected areas can become painful, pruritic, and malodorous. The disease course fluctuates between episodic remission and exacerbation aggravated by friction, heat, sweat, tight clothing, increased weight, and infection.<sup>3</sup>

Additionally, bacterial or fungal infection can be superimposed on the affected areas, convoluting diagnosis and complicating management of the disease. Longitudinal leukonychia has been described in approximately 70% of individuals with the disease and, if present, can aid in the diagnosis.<sup>3</sup>

## Differential Diagnosis

The clinical differential diagnosis of Hailey-Hailey disease includes candidiasis, inverse psoriasis, intertrigo, tinea cruris, contact dermatitis, seborrheic dermatitis, hidradenitis suppurativa, and erythrasma. Histologic differential diagnosis includes other intraepidermal acantholytic processes such as pemphigus vulgaris, Darier’s disease, and Grover’s disease. An extensive history and physical examination along with a biopsy, especially if little or no improvement is seen with treatment, help to support the diagnosis (**Table 1**).

A fungal infection, such as intertriginous candidiasis, may present clinically by the presence of satellite lesions with peripheral papules and pustules.<sup>9</sup> A potassium hydroxide stain will help to confirm the diagnosis, but care should be taken as a superimposed fungal infection can lead to misdiagnosis by masking the underlying Hailey-Hailey disease.

Inverse psoriasis presents in intertriginous areas, similarly to HHD. It presents as erythematous, sharply demarcated, smooth, non-scaly, moist plaques with or without maceration and fissures.<sup>10</sup> Typically, patients have a family history of psoriasis and psoriasiform lesions with evidence of typical psoriatic nail involvement, including onycholysis and nail pitting.<sup>11</sup>

Intertrigo clinically appears very similar to HHD, as erythematous plaques with maceration and inflammation of the skin folds. These lesions are prone to bacterial or fungal infections such as candida. A Wood’s light can help to distinguish a pseudomonal infection from cutaneous erythrasma caused by *C. minutissimum*. *Pseudomonas* fluoresces green under Wood’s light, while *C. minutissimum* fluoresces as coral red patches with well-defined borders.<sup>12</sup>

Tinea corporis typically presents clinically by the appearance of a raised and annular active border of pustules or vesicles with either central scale (in early lesions) or central clearing (in advanced lesions).<sup>13</sup> Tinea cruris may appear similar, as well-demarcated erythematous plaques with central clearing and elevated scaling borders that may be active with pustules or vesicles, and may be confirmed by KOH examination.<sup>14</sup>

## Treatment

HHD has no known cure, and treatment therapies are aimed at reducing exacerbations and increasing periods of remission. Many treatment modalities have been attempted, with most modalities demonstrating Level III evidence in the literature. Some patients are refractory to treatment, thus individual therapy must be tailored to each patient (**Table 2**).

General measures should be considered for each patient, such as avoidance of hot and humid weather, use of bleach or chlorhexidine baths, weight loss, and use of lightweight, loose clothing such as cotton. The use of absorbent pads, barriers, and drying agents such as zinc oxide, petrolatum, aluminum sulfate, and talcum powder may be used to keep skin dry and clean.<sup>15,16</sup>

First-line treatment should consist of a combination of topical antimicrobials and topical steroids.<sup>3,17,18</sup> Based on Level IIa and Level III evidence, clobetasol should be used for acute flares and topical tacrolimus for maintenance.<sup>19</sup> The topical antimicrobials that have shown some degree of success include clindamycin, gentamicin, mupirocin, and ketoconazole.<sup>3,17</sup>

Systemic therapy may be necessary if a patient fails the topical antimicrobial and topical steroid combination therapy. Doxycycline has been shown to be the most appropriate first-line oral antibiotic with Level IIa and Level III evidence.<sup>19</sup> Second-line oral therapy includes erythromycin, penicillin, and dapsone with limited Level III studies.

If a patient is refractory to therapy, additional therapies include surgical excision and botulinum toxin type A injections. These therapies have Level IIa and Level III evidence and have had some degree of success. Other treatment modalities include dermabrasion, NB-UVB, and laser therapy. These treatments have limited Level III evidence and have had limited success. Currently, there is a Phase II trial in Italy studying the use of afamelanotide, an analog of alpha-melanocyte stimulating hormone ( $\alpha$ -MSH), for the treatment of HHD.

## Conclusion

Hailey-Hailey disease is a rare disease that may be difficult to distinguish from other intertriginous diseases. HHD should be considered in patients with recurrent flares of intertriginous lesions. Diagnosis is more difficult if a superimposed bacterial and fungal infection is present. A biopsy and clinical features, such as longitudinal leukonychia, can help distinguish this disease. While there is no known cure, individualized treatments using a combination of antimicrobials and steroids are important to decrease patient morbidity, reduce flares, and limit complications.

**Table 1. Clinical differentiation of intertriginous dermatitides**

Condition	Clinical Differentiation
Hailey-Hailey Disease	<ul style="list-style-type: none"> <li>- Intertriginous erosive erythematous plaques</li> <li>- Crusting, maceration, and fissures</li> <li>- 2nd or 3rd decade of life, waxing and waning symptoms</li> <li>- Longitudinal leukonychia</li> </ul>
Intertriginous Candida	<ul style="list-style-type: none"> <li>- Satellite lesions with peripheral papules and pustules</li> <li>- Well-demarcated, erythematous patches</li> <li>- + KOH Prep</li> </ul>
Inverse Psoriasis	<ul style="list-style-type: none"> <li>- Erythematous, sharply demarcated plaques</li> <li>- Smooth, moist, macerated, +/- fissures</li> <li>- Absent scales</li> <li>- + Nail involvement</li> </ul>
Tinea Cruris	<ul style="list-style-type: none"> <li>- Well-demarcated erythematous plaques</li> <li>- Central clearing and elevated scaling borders</li> <li>- +/- Pustules or vesicles</li> </ul>
Erythrasma	<ul style="list-style-type: none"> <li>- Reddish-brown macules coalescing into patches</li> <li>- Well-defined borders</li> <li>- C. minutissimum - coral red fluorescence (Wood's)</li> <li>- Pseudomonas - green fluorescence (Wood's)</li> </ul>
Seborrheic Dermatitis	<ul style="list-style-type: none"> <li>- Sharply marginated erythematous eruption</li> <li>- + Erosions and fissures</li> <li>- +/- Yellow greasy scales</li> </ul>

**Table 2. Treatment and management of Hailey-Hailey disease**

Individualized Combination Therapy			Evidence Level
Topical Steroids	Acute flare	Clobetasol	IIA, III
	Maintenance	Tacrolimus	IIA, III
<i>plus</i>			
Antimicrobials	First line: topical	Clindamycin	IIA, III
		Gentamicin	
	Mupirocin		
	Ketoconazole		
Second line: systemic	Doxycycline	IIA, III	
	Dapsone	III	
	Erythromycin		
Penicillin			
<b>Refractory to Treatment</b>			
	Excision		IIA, III
	Botulinum toxin A		IIA, III
	Dermabrasion, NBUVB, Laser therapy		III
<b>General measures</b>			
	Bleach or chlorhexidine baths		V
	Weight loss		V
	Lightweight and loose clothing		V
	Barrier and drying agents		V
	Avoidance of hot and humid weather		V

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**Correspondence:** Miguel Villacorta, DO, MPH;  
Ph: 305-775-4688; F: 888-487-1106;  
miguel.villacorta@gmail.com

# A Rare Cause of a Solitary Facial Nodule: Primary Cutaneous CD4+ Small/Medium-Sized Pleomorphic T-cell Lymphoma

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

\*Second-year dermatology resident, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL

\*\*First-year dermatology resident, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL

\*\*\*Program Director, Dermatology Residency Program, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL

## Abstract

*Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL) is a very rare subset of cutaneous T-cell lymphoma characterized by the onset of a plaque or nodule on the head or neck that portends a favorable prognosis. We present a case of a 51-year-old woman who presented with a solitary nasal papule that was diagnosed as PCSM-TCL. Fewer than 250 cases of PCSM-TCL have been reported in the literature. We review the classification, literature, and treatment modalities of these rare, non-mycosis fungoides and non-CD30+ cutaneous T-cell lymphomas.*

## Introduction

First described in 1806 by the French dermatologist Jean-Louis Alibert, primary cutaneous T-cell lymphoma is defined as T-cell lymphoma with only cutaneous manifestations at the time of diagnosis.<sup>1</sup> Ninety percent of cases of primary cutaneous T-cell lymphoma are represented by either mycosis fungoides or primary cutaneous CD30-positive T-cell lymphoproliferative disorders (Table 1).<sup>2</sup> Outside of these two groups, cutaneous T-cell lymphomas can be categorized as either unspecified cutaneous T-cell lymphoma, adult T-cell leukemia/lymphoma, subcutaneous panniculitis-like T-cell lymphoma, or extranodal NK/T-cell lymphoma, nasal type.

The unspecified primary cutaneous peripheral T-cell lymphoma represents a heterogeneous group that does not fit into other subtypes. According to the World Health Organization-European Organization for Research and Treatment of Cancer (WHO-EORTC), this category encompasses three rare subtypes: primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAE-TCL), cutaneous gamma/delta T-cell lymphoma (CGD-TCL), and primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL).<sup>3</sup> Fewer than 250 cases of PCSM-TCL have been reported in literature.<sup>4</sup> We present a rare case of PCSM-TCL in a 51-year-old

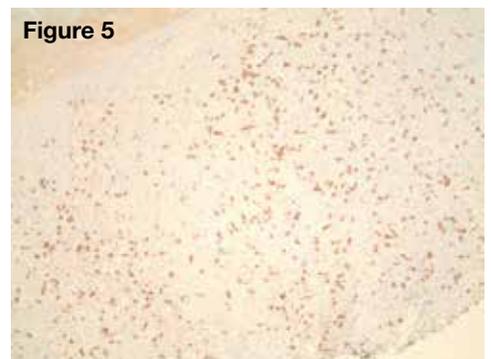
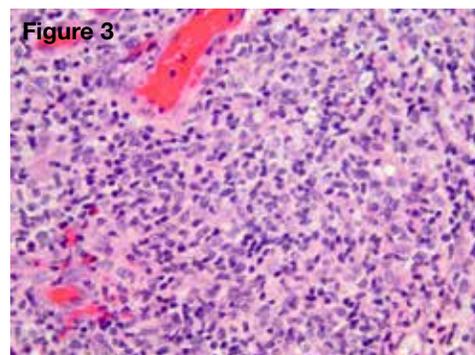
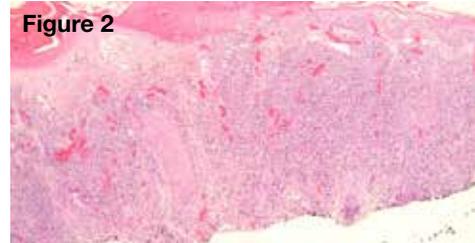
woman with a rapidly enlarging nasal papule and discuss the characteristics and findings of the subtypes of primary cutaneous peripheral T-cell lymphoma, unspecified.

## Case Presentation

A 51-year-old African American woman presented to the dermatology clinic with a rapidly enlarging lesion on the left side of her nose. The lesion erupted three months prior to presentation and was pruritic in nature. Medical history was noted for hypertension and hyperlipidemia, and her medications included hydrochlorothiazide and simvastatin. Family history was noncontributory. Physical examination revealed a well-defined, solitary, sharply demarcated, circular brown-pink papule measuring 0.5 cm on her left nasal ala (Figure 1). The physical examination did not reveal lymphadenopathy or hepatosplenomegaly.

Shave biopsy of the nasal lesion on low power revealed a dense dermal infiltrate with epidermal and adnexal exocytosis of lymphocytes, along with a Pautrier-like microabscess (Figure 2). Higher magnification revealed a pleomorphic infiltrate of small- and medium-sized T cells (Figure 3). The T cells were positive for CD3, CD2, CD25, and CD5. CD4 staining was strongly positive (Figure 4), and only rare CD8-positive cells were noted (Figure 5), with a CD4:CD8

ratio of greater than 10:1. ALK-1 was negative, and there was partial loss of CD7. C30 staining was negative, only highlighting a few scattered immunoblasts (Figure 6). CD20-positive B cells were noted, but they were rare. Positive T-cell gene rearrangement was appreciated by PCR. Complete blood count, basic metabolic profile, liver function tests, and serum protein electrophoresis were within normal parameters. Human T-cell lymphocytic virus types 1 (HTLV-1) and 2 DNA serologies were negative. Human immunodeficiency virus (HIV) was negative, and lactate dehydrogenase was within



**Table 1. Classification and frequency of cutaneous T-cell lymphomas<sup>3</sup>**

Types	Subtypes	Frequency
Mycosis fungoides		44%
Mycosis fungoides variants and subtypes	Folliculotropic	4%
	Pagetoid	< 1%
	Granulomatous slack skin	< 1%
Sézary syndrome		3%
Primary cutaneous CD30+ lymphoproliferative disorders	Primary cutaneous anaplastic large-cell lymphoma	8%
	Lymphomatoid papulosis	12%
Adult T-cell leukemia/lymphoma		2%
Subcutaneous panniculitis-like T-cell lymphoma		1%
Extranodal NK/T-cell lymphoma, nasal type		< 1%
Primary cutaneous peripheral T-cell lymphoma (unspecified)	Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma	< 1%
	Cutaneous gamma/delta T-cell lymphoma	< 1%
	Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma	2%

**Table 2. Differential Diagnosis of PCSM-TCL and Distinguishing Features<sup>4,5</sup>**

Differential Diagnosis	Shared Features with PCMS-TCL	Unique Features of PCSM-TCL
<b>Mycosis fungoides (MF)</b>	Atypical lymphocytes, epidermotropism	Lack of of evolving erythematous scaly patches and plaques; focal epidermotropism; nodular infiltrate in deep dermis/subcutis; absence of cerebriform nuclei; many mitotic figures
<b>Subcutaneous panniculitis-like T-cell lymphoma</b>	Atypical lymphocytes extend into subcutaneous fat	Usually not seen on legs; small-to-medium atypical lymphocytes; neoplastic cells lack cytophagocytosis; rim pattern around lipocytes
<b>T-cell pseudolymphoma</b>	Small, solitary plaque or nodule; lack of systemic features; mixed infiltrate; favorable prognosis with low rate of recurrence	Not associated with medication use, insect bites, immunologic disorders; TCR clonality with aberrant T-cell phenotypes; small-to-medium lymphocytes; less infiltrate of CD8+ cells, B cells, histiocytes
<b>Lymphomatoid papulosis</b>	History of spontaneously resolving lesions; CD30+ cells	Does not regress in 3 months; lower expression of CD30+ cells

**Table 3. Summary of the characteristics of non-mycosis fungoides and non-CD30+ cutaneous T-cell lymphomas<sup>3</sup>**

Type	Presentation	Phenotype/ Serology	Prognosis/Median Survival	Treatment
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma	Solitary papule on head or neck	CD3+, CD4+, CD8-, CD30-	Good; 5-year survival rate of 60%-80%	Radiotherapy, surgical excision
Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma	Localized or disseminated nodules with central ulceration	CD3+, CD4-, CD8+, CD45RA+ CD30±	Poor; 32-month survival (angioinvasion)	Combination chemotherapy
Cutaneous gamma/delta T-cell lymphoma	Disseminated necrotic nodules on extremities	CD2+, CD3+, CD4-, CD8-, CD5-, CD56+	Poor; 15-month survival (angioinvasion; hemophagocytic syndrome common)	Combination chemotherapy +/- radiotherapy
Adult T-cell leukemia/lymphoma	<u>Acute form</u> : leukemia, lymphadenopathy, organomegaly, hyperkalemia	HTLV-1+, CD3+, CD4+, CD8-, CD25+	<u>Acute form</u> : poor; aggressive, 2-week to 1-year survival	Systemic chemotherapy
	<u>Chronic and smoldering forms</u> : isolated skin lesions		<u>Chronic and smoldering forms</u> : longer survival	
Subcutaneous panniculitis-like T-cell lymphoma	Solitary or multiple nodules of legs, arms, trunk	TCR-alpha/beta+, CD3+, CD4-, CD8+, CD56-	Good; 5-year survival rate of 80% in alpha/beta+, CD8; if hemophagocytic syndrome (rare), then poor prognosis	Doxorubicin-based combination chemotherapy and radiotherapy
Extranodal NK/T-cell lymphoma, nasal type	Midfacial destructive midline tumor or multiple tumors	EBV+, CD2+, CD56+, CD3-epsilon+, CD3-	Poor; aggressive, 12-month survival	Systemic chemotherapy

normal limits. Computed tomography of the chest, abdomen, and pelvis showed no evidence of lymphadenopathy or further abnormalities. Bone marrow aspiration revealed no evidence of malignancy, and no Sézary cells were noted on flow cytometry.

The findings were most consistent with PCSM-TCL. The diagnosis was based upon a dense infiltrate of small- to medium-sized atypical cells, some reactive B cells, absence of prominent epidermotropism, CD4-positive immunohistochemistry, absence of CD30 staining, and lack of clinical lesions characteristic of mycosis fungoides (Table 2).

Treatment included a total of 35 Gy over 10 fractions of localized electron-beam radiation therapy, which achieved resolution of the nodule. Follow-up at one year demonstrated no evidence of recurrence.

## Discussion

### Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma

Primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma (PCSM-TCL) represents a very rare cause of cutaneous T-cell lymphoma and is associated with a favorable prognosis. In 1997, PCSM-TCL was recognized

as a distinct type of cutaneous T-cell lymphoma characterized by the presence of less than 30% large pleomorphic tumor cells, CD4-positive phenotype, and a lack of clinical features typical of mycosis fungoides.<sup>5</sup> In the recent WHO classification of cutaneous lymphomas, PCSM-TCL is included as a provisional entity under primary cutaneous peripheral T-cell lymphoma, unspecified. This rare neoplasm represents only 3% of all primary cutaneous T-cell lymphomas.<sup>5</sup>

Clinically, PCSM-TCL presents as a solitary plaque or nodule on the face, neck, or upper trunk. Infrequently, it can present with several papules, nodules or tumors.<sup>3</sup> In the largest case series reported, male-to-female ratio was equal, and the median age of onset was 53 years, very close to the age of our patient.<sup>7</sup>

Histologically, PCSM-TCL demonstrates a dense, diffuse or nodular infiltrate of CD4-positive T cells, often penetrating the subcutis, along with focal epidermotropism. The cell type generally consists of predominately small/medium-sized pleomorphic T cells, with less than 30% large pleomorphic cells.<sup>3</sup> If greater than 30% large pleomorphic cells are noted, an alternative diagnosis should be considered. For example, peripheral T-cell lymphoma, not otherwise specified, is characterized by greater than 30% large pleomorphic T cells and has a

much poorer prognosis than PCSM-TCL.<sup>3</sup> A rich infiltrate of reactive B cells is often noted, as was seen in our patient.<sup>8</sup> Further, histiocytes, plasma cells, and eosinophils can often be seen.<sup>2,9</sup> Immunohistochemistry is significant for positive CD3 and CD4, while CD8-positive cells are rare. CD30 is characteristically negative, which helps to distinguish it from lymphomatoid papulosis.<sup>3</sup> CD25, which is often positive in adult T-cell leukemia/lymphoma, was positive in our patient. Although usually negative in PCSM-TCL, case series have reported CD25 positivity. It is of utmost importance in the presence of CD25 positivity to check HTLV-1 and HTLV-2 to rule out adult T-cell leukemia/lymphoma, which follows an aggressive course with a poor prognosis (Table 3).<sup>4</sup>

The differential diagnosis includes localized mycosis fungoides, T-cell pseudolymphoma, subcutaneous panniculitis-like T-cell lymphoma and lymphomatoid papulosis (Table 2).<sup>4,8</sup> Mycosis fungoides can be distinguished by the presence of pronounced epidermotropism and a band-like lymphocytic infiltrate. However, with PCSM-TCL the tumor infiltrates extend to the deeper dermis and even subcutis, and mitotic figures are often more common.<sup>8,10,11</sup> Distinguishing PCSM-TCL from T-cell pseudolymphoma can be done by identifying aberrant T-cell phenotype

(present in 60% to 70% of PCSM-TCL cases) plus clonality; there are only reactive T cells in T-cell pseudolymphoma.<sup>3,8</sup>

For the most part, prognosis is favorable, with a five-year survival rate of 60% to 80%.<sup>7</sup> Improved survival is associated with solitary lesions, size less than 3 cm, and a CD4-predominant phenotype, all features demonstrated in our patient.<sup>5,8</sup> PCSM-TCL remains the only subtype of unspecified primary cutaneous peripheral T-cell lymphoma with a favorable prognosis. This is debatable, however, as aggressive behavior has been reported in 33 patients, with 13 fatalities.<sup>4</sup> Because of this controversial prognosis, PCSM-TCL remains a provisional subcategory in the WHO-EORTC classification scheme.<sup>3,4</sup> Factors associated with aggressive behavior include loss of CD2 expression (which was maintained in our patient), low numbers of CD8-positive cells, high T-cell proliferation rates as demonstrated by Ki-67 positivity, and variable expression of CD4.<sup>4</sup>

The optimal treatment of PCSM-TCL has yet to be elucidated. Treatment options include surgical excision, topical or systemic glucocorticoids, localized psoralen plus ultraviolet-A range (PUVA) bath therapy, or localized radiotherapy for solitary lesions.<sup>3,4,8</sup> Localized radiotherapy achieved an 83% response rate in one study, and also proved to be effective therapy in our patient.<sup>12</sup> Systemic chemotherapy in localized cases has yet to be as successful as other treatment modalities, with doxorubicin-based chemotherapy having a mere 40% complete remission rate.<sup>12</sup> Topical mechlorethamine with topical corticosteroid, a treatment regimen often used in mycosis fungoides, has been found to be effective as well.<sup>4</sup> One case study reported complete clearance of a solitary lesion on doxycycline 200 mg daily for 21 days, possibly via caspase-3 activation leading to cell apoptosis, among other cell mechanisms.<sup>6</sup> Spontaneous regression without any therapy has also been described.<sup>7,9</sup> In patients with generalized disease, cyclophosphamide, interferon alpha, etretinate, and combination chemotherapy have been reported as effective therapy.<sup>3,8,10</sup>

#### **Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma**

Primary cutaneous aggressive epidermotropic CD8+ T-cell lymphoma (PCAE-TCL), representing less than 1% of all cutaneous T-cell lymphomas, exhibits CD8-positive cytotoxic T cells, aggressive clinical behavior and a poor prognosis.<sup>3,13</sup> Clinically, PCAE-TCL often presents as eruptive papules or nodules with ulceration centrally. Disseminating to mucosal and extranodal sites such as the lung, testis, or central nervous system is not uncommon. Despite the ability to disseminate, lymph nodes often lack metastases.<sup>3,13</sup>

On histology, epidermotropism and necrotic keratinocytes are often noted, along with angioinvasion.<sup>13</sup> Immunophenotype demonstrates positivity of CD3 and CD8 while lacking CD4 and CD7. Cases of CD30-positivity have been reported, unlike in PCSM-TCL

(**Table 3**).<sup>3</sup> Prognosis is extremely poor, with most patients surviving a little over one year after diagnosis. Treatment includes chemotherapy with a doxorubicin-based regimen.<sup>13</sup>

#### **Cutaneous gamma/delta T-cell lymphoma**

Like PCAE-TCL, cutaneous gamma/delta T-cell lymphoma (CGD-TCL) presents as an aggressive, disseminated plaque or ulcerative necrotic nodules, which tend to be localized to the extremities. Like PCAE-TCL, extracutaneous sites are frequently involved but lymph nodes are unaffected.<sup>13</sup>

Histology is significant for patterns of epidermotropism, dermal involvement or a subcutaneous infiltrate similar to a panniculitis. Angioinvasion is not uncommon, as in PCAE-TCL, and apoptosis and necrosis may be present.<sup>3</sup> Immunohistochemistry is noted for positivity of CD2, CD3 and CD56 with absence of CD4, CD8, and CD5. CD56 positivity can help differentiate CGD-TCL from subcutaneous panniculitis-like T-cell lymphoma (**Table 3**).<sup>13</sup>

Prognosis is poor, with a median survival of 15 months. In patients with panniculitis-like tumors, a hemophagocytic syndrome may occur, which is unique to this subtype but can often be seen in subcutaneous panniculitis-like T-cell lymphoma.<sup>3</sup> Treatment includes multimodalities with chemotherapy and radiation.<sup>13</sup>

### **Conclusion**

PCSM-TCL is a very rare cause of a solitary nasal papule, with only a few published case series and reports to describe its clinicopathologic features, prognosis and treatment. Having a broader differential diagnosis for a solitary nasal papule beyond basal cell carcinoma or fibrous papule is very important to help the dermatopathologist and the dermatologist work together to reach the correct diagnosis. This heterogeneous disease with various entities affecting its prognosis has a wide variety of treatments that for the most part have a favorable outcome. Nevertheless, treating this lesion hinges on the astute clinician placing this entity in the differential diagnosis based upon the clinical scenario.

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### Correspondence:

Christina Steinmetz-Rodriguez, DO;  
TinaStein@aol.com

# A Case of Median Nail Dystrophy Treated with Poly Urea-Urethane Solution

Sergey Petrosian, BS,\* Shane Meehan, MD,\*\* Stephanie Lasky, DO,\*\* Peter Saitta, DO\*\*\*

\*Medical Student, 4<sup>th</sup> year, New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY

\*\*Dermatology Resident, 2<sup>nd</sup> year, St. John Episcopal Hospital, Far Rockaway, NY

\*\*\*Dermatologist and Clinical Instructor, Ronald O. Perelman Department of Dermatology, New York University School of Medicine, New York, NY

## Abstract

We present a case of median canaliform nail dystrophy (MND) cured with poly-ureaurethane 16% solution (Nuvail®, Innocutis Holdings LLC, Charleston, South Carolina). **Case:** A 59-year-old Caucasian male with a six-year history of a disfigured right thumb nail and no other co-morbidities or relevant history presented to the clinic. Physical examination showed a midline fissure in the right thumbnail that ran from the lunula to the distal nail fold, accompanied by transverse fissuring. The remainder of the fingernails were normal. The history and physical examination lead to a diagnosis of median nail dystrophy. **Management and Outcome:** There is no standard therapy for MND. The patient was started on poly-ureaurethane 16% solution applied once a day. Follow-up visits were scheduled at one-month intervals. The patient's nail showed a gradual improvement and the condition was cured in three months' time. **Discussion:** A mechanism of action for the poly-ureaurethane 16% solution used to treat the patient is proposed. **Conclusion:** We believe the mechanism was two fold. First, the solution allowed a protective physical barrier for the nail to prevent micro and macro trauma. Second, the properties of the ureaurethane helped promote the growth of new healthy nail.

## Introduction

Median canaliform nail dystrophy (MND) is also known as dystrophia unguium mediana canaliformis and median canaliform dystrophy of Heller.<sup>1</sup> It is an unusual condition that typically affects the thumb, but can affect other fingers or toes. It is characterized by a median longitudinal canal or splitting of the nail. It is accompanied by small lateral cracks or fissures that project from the central canal toward the nail edge. These findings give the typical fir-tree pattern appearance.<sup>2</sup> The diagnosis is confirmed solely on clinical findings. Onset is usually in adulthood. Typically, patients will have had the problem for a long time and have no explanation as to why the issue is present. It is thought that the condition may be related to repetitive trauma such as picking or pushing of the cuticle. Habit-tic deformity is another nail condition with a similar presentation to MND and is also thought to be caused by repetitive unnoticed external trauma to the nail.<sup>3</sup> It is very difficult to distinguish the two, but if there is an inverted fir-tree pattern, this is more suggestive of MND. However, it is sometimes thought that the two are variants of the same disease process.<sup>3</sup>

Nail deformities frequently have unknown etiologies and can present on their own, as manifestations of cutaneous or systemic diseases or as side effects from certain drugs. The pathophysiology of MND is unclear and speculative, and there are no definitive diagnostic tests. There is also no standard therapy for treatment. All of these factors make the management of patients with median nail dystrophy difficult. Our findings are unique because it is the first time that a case of MND has been treated with poly-ureaurethane 16% nail solution and a complete cure has been documented.

## Case Report

A 59-year-old Caucasian male presented to our clinic complaining of a disfigured right thumb nail for a duration of six years. He stated that the nail initially cracked down the center and then progressively worsened. The patient also

mentioned that there were times where he believed it was getting better, but then would regress. There was no associated trauma, nor were there any complaints of pain, weakness, or numbness. The patient had no relevant medical, surgical, social or family history, and a review of systems was non-contributory.

Physical examination demonstrated a midline fissure in the right thumbnail that ran from the lunula to the distal nail fold, accompanied by transverse fissuring. There was also a yellow discoloration (**Figure 1**). The remainder of the fingernails were normal. There was no clubbing, cyanosis, or edema present, and strength and sensation were within normal limits. Based on the clinical examination, the lack of underlying systemic disease, and the absence of reported trauma, we diagnosed the patient with median canaliform nail dystrophy.

## Management and Outcome

Our patient was treated with poly-ureaurethane 16% solution applied to the affected nail one time a day for a duration of three months. During that span, the nail showed a gradual improvement, with the median nail dystrophy eventually resolving completely (**Figure 2**). The patient began using the medication within five days of the initial visit. Follow-up appointments were made at one-month intervals. After the first month, there was some improvement in the nail, the midline fissure was less pronounced and the nail base near the lunula seemed to be growing normal, healthy nail. The second visit showed significant improvement in the nail. The majority of the right thumb nail looked normal, with only the distal fourth of the nail still showing the pathology. At the third and final visit, the nail looked completely normal, with no trace of any fissures. During the treatment period, the patient had no complaints and noted no side effects from the medication.

## Discussion

The pathophysiology of MND is unknown. However it is theorized that it is the result

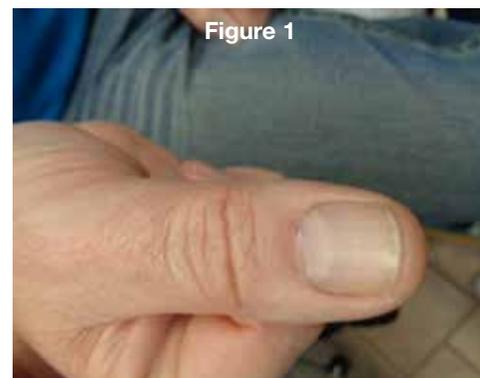


Figure 1



Figure 2

of a temporary defect in the nail matrix after dyskeratinization, hindering normal nail formation. MND has been shown to be associated with self-inflicted or job-related trauma to the nail.<sup>4</sup> Familial cases have been reported as well.<sup>5</sup>

MND development has also been reported in patients treated for acne with isotretinoin.<sup>6</sup>

MND has no standard treatment because no therapy has consistently worked and because

it often will resolve on its own without intervention.<sup>1</sup> If a medication or other offending agent is the presumed cause, removing the agent will usually result in resolution of the MND.<sup>6</sup> Possible treatments include triamcinolone acetonide injections into the nail fold and topical 0.1% tacrolimus ointment.<sup>4,7</sup> In our literature search, we were unable to find any reports of poly-ureaurethane solutions being used as a treatment for nail disorders.

We successfully treated our patient with a once-a-day application of poly-ureaurethane 16% nail solution. We believe the etiology for our patient's MND was continuous, unnoticed micro-trauma. Poly-ureaurethane 16% nail solution coats and sticks to the nail surface, providing a protective layer that prevents direct injury and scraping. Nails are somewhat permeable and allow the solution to infiltrate intercellular spaces and bind to keratin. This creates a strong water-resistant shield, while also providing mechanical support to the nail. It has been shown that poly-ureaurethane can act like scaffolding in normal tissue and binds proteins like albumin, hemoglobin, thrombin, fibrinogen, fibronectin, complement components, and immunoglobulins.<sup>8</sup> In the nail, we postulate that the poly-ureaurethane absorbs and adheres to keratin, improving the integrity of the nail and thereby preventing unnoticed trauma to the nail plate.

The functionality of the polyurethane in different applications depends on the chemistry of the polymer. Manufacturers can alter the chemistry of poly-ureaurethanes for different purposes. In experiments done with polyurethanes and vascular grafts, hydrophobic polyurethane urea grafts were found to possess superior cellular-migration characteristics versus their hydrophilic counterparts.<sup>10,11</sup> The polyurethane urea solution we used is also hydrophobic in nature.<sup>8</sup> We believe that a similar mechanism takes place in the nail, whereby the nail solution promotes cellular migration from the nail matrix to the nail plate, augmenting the formation of new, healthy nail.

## Conclusion

In conclusion, we believe the mechanism of poly-ureaurethane 16% nail solution in the MND was twofold. First, it provided physical reinforcement and a barrier for the nail. Second, it promoted the formation and growth of new healthy nail.

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**Correspondence:** Sergey Petrosian;  
Spetrosi@nyit.edu

# Morphea in Post-irradiated Skin of a 65-year-old Female with Breast Cancer: A Case Report and Review of the Literature and Treatment Options

Mayha Patel, DO,\* Teresa Ishak, DO,\*\* John Merrill, BS,\*\*\* David Horowitz, DO, FAOCD\*\*\*\*

\*Dermatology Resident, 2nd year, Chino Valley Medical Center/Western University, Chino, CA

\*\*Dermatologist, Private Practice, Fullerton, CA

\*\*\*Medical Student, 3<sup>rd</sup> year, Western University of Health Sciences College of Osteopathic Medicine, Pomona, CA

\*\*\*\*Faculty, Dermatology Residency Program, Chino Valley Medical Center/Western University, Chino, CA

## Abstract

*Morphea is a localized form of scleroderma presenting with sclerotic erythematous plaques limited to the skin with no internal organ involvement. A specific type of morphea called post-irradiation morphea occurs in patients one month to three years after radiation treatment. This is a very rare and under-recognized condition that is often misdiagnosed. We report the case of a 62-year-old female with post-irradiation morphea and review the pathogenesis and treatment options in addition to its similarities and differences with radiation-induced fibrosis.*

## Introduction

Morphea, or localized scleroderma, is a localized, cutaneous form of scleroderma that lacks the systemic features and organ involvement characteristic of progressive systemic scleroderma. It typically presents as a violaceous to hypopigmented plaque that progresses to induration with a smooth and shiny surface as sclerosis develops. Possible etiologic triggers of morphea include traumatic injury, infection, chemical exposure, and radiation exposure. The incidence of morphea of any etiology in the general population is 2.7 per 100,000 per year.<sup>1</sup>

Post-irradiation morphea (PIM) is a rare condition that appears abruptly with erythema and induration followed by fibrosis in women one month to three years status post-radiation treatment of breast cancer.<sup>1</sup> The first case of morphea as a complication of radiotherapy for cancer was reported by Colver et al. in 1989.<sup>2</sup> Since then, several cases of PIM have been reported, and the incidence of PIM is estimated to be approximately 1 in 500 patients.<sup>2</sup>

Radiation-induced morphea (RIM) of the breast should be distinguished from PIM. RIM occurs anywhere from one to 12 months, and possibly up to 32 years, after radiation therapy.<sup>4</sup> In addition, the involved area of PIM typically correlates with a previous radiotherapy treatment field, whereas in RIM, involvement is always seen both within and beyond the radiotherapy field.<sup>4</sup>

We report a case of post-irradiation morphea (PIM) following local irradiation of breast cancer and review the various treatment approaches found in the literature.

## Case Report

A 62-year-old female was diagnosed with breast cancer in June of 2008 and immediately sent for lumpectomy and sentinel lymph node dissection on July 2, 2008. All nodes were negative during this procedure. The patient then underwent radiation therapy from October to November of 2008, five days a week for seven weeks. After this therapy, the patient was started on tamoxifen but was only able to tolerate about two months of treatment due to side effects. She discontinued this medication and made the decision not to continue with any systemic treatment. The patient had an uncomplicated period of two years from the cessation of her therapy in 2008. However, in 2010 she began to develop thickening of the skin under her left and right breast in addition to multiple erythematous lesions under bilateral breast folds. The patient was subsequently referred to our dermatology clinic by her oncologist, who was concerned the rash may be evidence of metastatic carcinoma.

On clinical exam, the patient had multiple blanchable, sclerotic, erythematous, palpable plaques under her bilateral breast folds (**Figures 1, 2**). A punch biopsy was consistent with morphea, showing thickened collagen bundles in the reticular dermis and superficial subcutaneous adipose tissue and a superficial and deep perivascular and interstitial lymphoplasmacytic infiltrate (**Figure 3**). The patient was started on clobetasol ointment applied once daily, with significant improvement.

## Discussion

Post-irradiation morphea was first described in 1905 as a condition that develops after exposure to radiographs.<sup>3</sup> However, it was not until 1989 that Colver et al. recognized PIM as a complication of radiotherapy for cancer.<sup>2</sup> There has been no published data on the risk factors involved in the development of PIM nor on a linear relationship to radiation dose.<sup>4</sup> One proposed theory for the development of PIM is that radiation exposure may activate clonal fibroblasts, resulting in autoimmunity. An increase in cytokine production, such as transforming growth factor- $\beta$  (TGF- $\beta$ ), has been found.<sup>1</sup> This response results in an increase in glycosaminoglycan production, collagen synthesis and extracellular matrix protein secretion. TGF- $\beta$  is secreted by platelets, macrophages and T-lymphocytes, and an increase in the binding of platelet-derived growth factor (PDGF) to scleroderma fibroblasts has been observed after TGF- $\beta$  expression. This binding of PDGF leads to an increased growth of scleroderma fibroblasts.<sup>1</sup> Another study proposes the theory that these radiation-induced neoantigens that occur through direct effects on cellular proteins are recognized months to years later by B and T cells.<sup>5</sup> This recognition produces a local inflammatory response that results in the release of growth factors and other cytokines that go on to stimulate the production of excess collagen by fibroblasts.

PIM is commonly misdiagnosed as radiation-induced fibrosis (RIF), which is a much more common condition, believed to occur in about 23% of breast cancer patients given radiation treatment.<sup>6</sup> There are several differences between



Figure 1



Figure 2

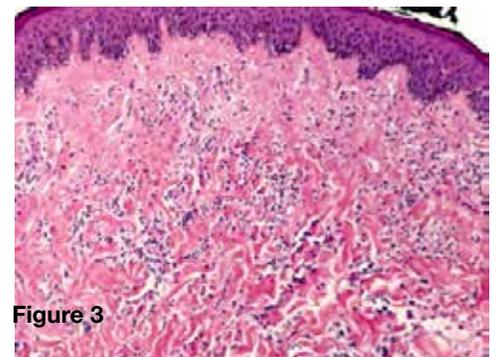


Figure 3

**Table 1. Histologic and clinical findings of PIM and RIF**

Disease	Clinical Findings	Etiology	Histology
Post-irradiation Morphea (PIM)	<ul style="list-style-type: none"> <li>- Abrupt onset</li> <li>- Two phases:               <ol style="list-style-type: none"> <li>1. inflammatory: erythema, induration</li> <li>2. "burnt-out": induration, fibrotic retraction, pigmentation</li> </ol> </li> <li>- Primarily a dermal fibrosis</li> <li>- Occurs 1 month to 3 years after exposure</li> <li>- Can expand beyond the field of radiation exposure</li> </ul>	<ul style="list-style-type: none"> <li>- Radiation-induced neoantigen</li> <li>- Neoantigen later recognized by B and T cells, stimulating TGF-<math>\beta</math></li> <li>- TGF-<math>\beta</math> strongly induces fibroblast activation, collagen synthesis, excessive fibrosis</li> <li>- PDGF binds to scleroderma fibroblasts, causing increased fibroblast growth</li> </ul>	<ul style="list-style-type: none"> <li>- Thickened collagen bundles in reticular dermis and superficial subcutaneous adipose tissue</li> <li>- superficial and deep perivascular and interstitial lymphoplasmacytic infiltrate in subcutaneous tissue underlying breast tissue</li> </ul>
Radiation-induced Fibrosis (RIF)	<ul style="list-style-type: none"> <li>- More common</li> <li>- Occurs within 3 months of exposure</li> <li>- Primarily a deep subcutaneous and fascial fibrosis</li> <li>- No erythema or induration</li> <li>- Does not expand beyond the field of radiation exposure</li> </ul>	<ul style="list-style-type: none"> <li>- Overactive signaling via PDGF receptor beta and V-abl Abelson murine leukemia viral oncogene homolog 1 (cAbl)</li> </ul>	<ul style="list-style-type: none"> <li>- Little or no inflammatory infiltrate</li> <li>- Differentiation of fibroblasts into postmitotic fibrocytes</li> <li>- Changes in vascular connective tissue</li> <li>- Excessive production and deposition of extracellular matrix proteins and collagen</li> </ul>

**Table 2. Therapeutic options for PIM**

Medication	Effect on Morphea	Mechanism of Action
UVA-1	<ul style="list-style-type: none"> <li>- Reduction in sclerotic plaques</li> <li>- Increase in skin elasticity</li> <li>- Decrease in skin thickness as measured by ultrasound</li> </ul>	<ul style="list-style-type: none"> <li>- Levels of MMP-1/2/3 increase after UVA1 treatment</li> <li>- Increase in collagenase mRNA and protein expression in fibroblasts</li> <li>- Increase in collagen metabolism</li> <li>- Increased level of <math>\alpha</math>-melanocyte-stimulating hormone (<math>\alpha</math>-MSH)</li> </ul>
Combination of calcipotriol ointment with low-dose UVA-1	<ul style="list-style-type: none"> <li>- Morphea fibroblasts have an increased sensitivity to vitamin D<sub>3</sub> receptors, leading to inhibition of proliferation</li> <li>- Positive synergistic interference of both modalities</li> </ul>	<ul style="list-style-type: none"> <li>- Levels of MMP-1/2/3 increase after UVA1 treatment</li> <li>- Increase in collagenase mRNA and protein expression in fibroblasts</li> <li>- Increase in collagen metabolism</li> <li>- Increased level of <math>\alpha</math>-melanocyte-stimulating hormone (<math>\alpha</math>-MSH)</li> <li>- Calcipotriol causes an alteration of collagen and fibronectin synthesis as well as inhibition of fibroblast proliferation</li> </ul>
Tyrosine kinase inhibitor (imatinib)	<ul style="list-style-type: none"> <li>- Decrease in skin thickness</li> <li>- Decrease in myofibroblast numbers</li> <li>- Extracellular matrix accumulation</li> </ul>	<ul style="list-style-type: none"> <li>- Blocks the PDGF receptor and inhibits the TGF-<math>\beta</math> and PDGF-induced response in fibroblasts</li> </ul>

PIM and RIF. On histology, RIF lacks an inflammatory infiltrate and is primarily a deep subcutaneous and fascial fibrosis, whereas PIM is a localized scleroderma of primarily dermal fibrosis. PIM occurs one month to three years after radiation exposure, whereas RIF usually occurs in the first three months after treatment.<sup>6</sup> In addition, PIM is often abrupt in onset, with erythema and induration seen in the first phase of the condition, which is not observed in RIF.<sup>4,6</sup> Finally, PIM usually begins within the field of

radiation and in about 20% of cases may extend beyond that field, while RIF does not spread past the radiation site.<sup>6</sup> The different histologic and clinical findings of PIM and RIF are summarized in **Table 1**.

#### Differential Diagnosis

Other important differential diagnostic considerations include acute, subacute, and chronic radiation dermatitis, sclerosing post-irradiation panniculitis and radiation recall dermatitis, which is the recalling by skin of previous radiation exposure in response to the administration of certain response-inducing drugs.

## Histology

In PIM, the sclerosing changes seen clinically are thickened collagen bundles in the reticular dermis and superficial subcutaneous adipose tissue. The inflammatory changes are characterized by a superficial and deep perivascular and interstitial lymphoplasmacytic infiltrate, which is also seen in the subcutaneous tissue and underlying breast tissue<sup>7,8</sup> (Figure 3).

In radiation-induced fibrosis, an enhanced synthesis and deposition of the interstitial collagens, fibronectin and proteoglycans have been seen in fibroblast tissue in addition to differentiation of fibroblasts into postmitotic fibrocytes. These changes are due to radiation-induced modulation of the fibroblast-cell system to an abnormal proliferation of fibroblasts.<sup>7,8</sup>

## Treatment

Mild treatments for early lesions of PIM include topical and intralesional steroid creams and oral antibiotics. High-dose UVA1 treatment for localized scleroderma was first conducted by Stege *et al.* in 1997.<sup>9</sup> They found positive effects in terms of skin thickness and elasticity as well as increased levels of  $\beta$ -melanocyte-stimulating hormone ( $\beta$ -MSH), which would explain the normalization of skin color post treatment.<sup>10,11</sup> Medium-dose UVA1 treatment was no less effective than high-dose treatment and was significantly superior to UVB treatment and low-dose UVA1, with effects seen even in darker skin tones. UVA irradiation results in localized immunosuppression and remodeling of dermal collagen as it penetrates deeper into the skin, particularly by induction of matrix metalloproteinases, which are collagenases that initiate the cleavage process of the main collagen found in the skin.<sup>10,11</sup>

There have been several reports on success of combination treatment with calcipotriol ointment and UVA1 irradiation in the management of morphea. It has been shown that morphea fibroblasts have an increased sensitivity to vitamin D<sub>3</sub> receptors, leading to inhibition of proliferation and a positive synergistic interference of both modalities when given in combination. It must be noted, however, that the application of topical calcipotriol should not be performed two hours prior to or after phototherapy so as to avoid adverse interactions with UV radiation.<sup>12,13</sup>

Other therapeutic options are calcineurin inhibitors, heparin-containing creams and the tyrosine kinase inhibitor imatinib. Imatinib blocks the PDGF receptor and inhibits the TGF- $\beta$  and PDGF-induced response in fibroblasts, which play a key role in the pathophysiology of PIM.<sup>14</sup> In patients who are treated with imatinib, a decrease in skin thickness, myofibroblast numbers and extracellular matrix accumulation is seen.<sup>12</sup> Total excision of the area can also be conducted. For extreme cases of severe breast pain, a total mastectomy to alleviate the symptoms is often required. In other patients, the disease can be self-limiting, with spontaneous gradual softening of the skin. The therapeutic options are reviewed in Table 2.

Any treatment modality should be administered promptly to give the best result; however, there is little information on the overall outcome of these treatments in PIM. PUVA therapy itself does not completely reverse fibrosis and atrophy but instead causes distinct skin softening and therefore reduction in pruritus, pigmentation and skin tightness. Most skin changes may be improved within a few months to a few years, but pigmentation usually persists.

## Conclusion

Post-irradiation morphea is a rare but potential complication after radiotherapy for cancer. This skin disease occurs months to years after treatment, and is associated with remarkable morbidity and pain as well as cosmetic changes that are often very troublesome to patients. Researchers still do not know the relationship between the dosage of radiation and the severity of the induced morphea. For proper management and treatment, dermatologists and radiation oncologists should be aware that this condition may lead to the mistaken diagnosis of local tumor recurrence.

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**Correspondence:** Mayha Patel, DO; [mayhapatel@gmail.com](mailto:mayhapatel@gmail.com)

# Neoadjuvant Targeted Therapy for Locally Advanced Orbital Basal Cell Carcinoma: A Case Presentation and Discussion

Madeline Tarrillion, DO,\* Jennifer DePry, DO,\*\* Jeremy Bordeaux, MD,\*\*\* Jenifer Lloyd, DO\*\*\*\*

\*Dermatology Resident, 1<sup>st</sup> year, University Hospitals Regional Medical Center, Cleveland, OH

\*\*Dermatology Resident, 3<sup>rd</sup> year, University Hospital Regional Medical Center, Cleveland, OH

\*\*\*Director, Mohs Micrographic and Dermatologic Surgery, University Hospitals Case Medical Center, Cleveland, OH

\*\*\*\*Program Director, University Hospitals Regional Medical Center Dermatology Residency, Cleveland, OH

## Abstract

**Background:** Vismodegib is an FDA-approved, emerging therapy for metastatic and locally advanced basal cell carcinoma. **Objective:** We present a case of a locally advanced orbital basal cell carcinoma where vismodegib was used as neoadjuvant therapy. **Methods:** This patient received 11 months of vismodegib. **Results:** The tumor size greatly decreased; however, the patient had to stop vismodegib due to the side effects. The patient then developed an ocular infection and corneal ulcer, resulting in orbital exenteration. **Limitations:** This is a case report of one patient. **Conclusion:** Vismodegib is a new therapy for metastatic and locally advanced basal cell carcinoma; however, it currently has limitations that may discourage its use.

## Introduction

Vismodegib was FDA-approved in January 2012 for metastatic basal cell carcinoma and locally advanced basal cell carcinoma.<sup>1</sup> The latter is characterized by large tumor size, multiple lesions, or locally recurrent disease not appropriate for surgical treatment.<sup>2</sup> Vismodegib is an antagonist of the hedgehog pathway, which has been found to be activated in basal cell carcinoma, leading to cellular proliferation.<sup>2</sup> Vismodegib may serve an important role in the future treatment of metastatic and locally advanced basal cell carcinoma. We present a case of locally advanced orbital basal cell carcinoma where vismodegib was used as neoadjuvant therapy to assist in shrinking the tumor prior to surgery in the efforts of sparing the eye.

## Case Presentation

A 56-year-old man presented with a 2 cm x 3 cm x 4 cm ulcerated plaque with a pink, raised border involving the left medial canthus, and upper and lower eyelids (Figure 1). A biopsy of the left lower eyelid demonstrated a nodular proliferation of atypical basaloid cells within the dermis with peripheral nuclear palisading, stromal mucin, tumor-stromal clefting, and focal ulceration consistent with nodular basal cell carcinoma (Figure 2). An MRI of the brain, sinuses and orbits with and without

contrast revealed abnormal soft tissue along the anteromedial aspect of the left orbit, extending over the proximal left nasofrontal region with no evidence of paranasal sinus involvement or intracranial metastatic disease.

The patient was referred for Mohs micrographic surgery consultation. Treatment options were discussed, including Mohs micrographic surgery, which would likely sacrifice the eye, targeted therapy alone with vismodegib, and neoadjuvant therapy with vismodegib followed by Mohs micrographic surgery.

We initiated vismodegib 150mg/day with the plan that the patient would remain on vismodegib until the tumor stopped responding or the patient could no longer tolerate the side effects of the medication. At that point, surgery could be performed, potentially reducing the surgical

defect and hopefully preserving the eye.

The patient completed 11 months of vismodegib with decrease in tumor size and improvement of ulceration (Figures 3, 4 - post six months' treatment). Throughout the treatment period, the patient experienced dysgeusia (disturbance of taste), alopecia, fatigue, nausea, and significant weight loss. After 11 months of treatment, the patient could no longer tolerate the side effects, and vismodegib therapy was discontinued.

A month later, the patient developed an ocular infection complicated by a severe corneal ulcer, and the patient underwent an orbital exenteration with paramedian forehead flap. The patient is currently healing well six months after surgery, and is planning on reconstruction with prosthetic rehabilitation in the near future.

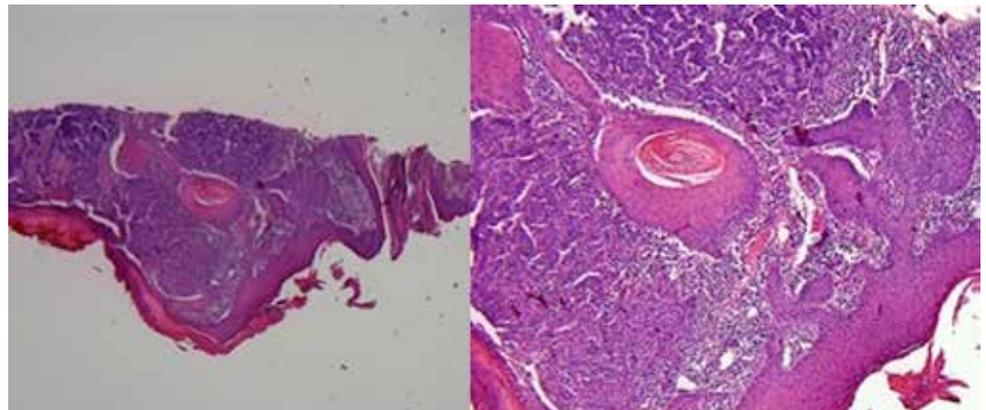


Figure 2. Biopsy of left lower eyelid, revealing nodular basal cell carcinoma (40x, 100x).



Figure 3. Post six months of vismodegib.

Figure 4. Initial presentation vs. post six months of treatment.



Figure 1. Ulcerated plaque (2 cm x 3 cm x 4 cm) with a pink, raised border involving the left medial canthus and upper and lower eyelids.

## Discussion

Most basal cell carcinomas involve alterations in the hedgehog signaling pathway, resulting in its activation and uncontrolled proliferation of cells. Most commonly, 90% of basal cell carcinomas are due to loss of function of the tumor suppressor gene patched (PTCH1), which inhibits the signaling activity of smoothened (SMO). In 10% of basal cell carcinomas, there is also an activating mutation in smoothened.<sup>3</sup> SMO activates the hedgehog pathway through downstream activation of GLI1.<sup>4</sup> Vismodegib is the first, FDA-approved, small-molecule, hedgehog pathway inhibitor. It inhibits SMO, thereby preventing downstream signaling of the pathway.<sup>3</sup>

Vismodegib is FDA-approved for the treatment of adults with metastatic or locally advanced basal cell carcinoma, when it is inoperable or when surgery is inappropriate. In a phase II trial of vismodegib, patients with metastatic and locally advanced BCC showed response rates of 30% and 43%, respectively. Response was defined as a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration if present at baseline.<sup>1</sup>

In several studies of vismodegib use, multiple side effects were commonly experienced, including muscle spasms or cramps, alopecia, dysgeusia (alteration of taste), weight loss, fatigue, nausea, decreased appetite, and diarrhea. While these adverse effects were generally regarded as minor, the necessary chronic use of vismodegib and, therefore, the persistent side effects commonly led patients to discontinue therapy.<sup>1</sup> These chronic adverse effects potentially limit the long-term use of vismodegib.

Other limitations hindering the chronic use of vismodegib include the possibility of tumor skip areas (persistent tumor in clinically "cured" skin), acquired resistance, increased risk of squamous cell carcinomas, and cost-inefficacy, with an average monthly cost of \$7,500 per month.<sup>4</sup>

With the development of vismodegib, there have been a few case reports and a small clinical trial evaluating neoadjuvant targeted therapy followed by surgery. This small clinical trial found that vismodegib needed to be used for at least three months to elicit a response. It found that vismodegib use reduced the surgical defect area by 27% for the 11 patients that underwent surgery following vismodegib. Finally, it showed that clinically resolved lesions do not necessarily correlate with histologic cure.<sup>5</sup>

Another study was performed in seven patients with periocular and orbital basal cell carcinoma in which the mean treatment duration was 11 weeks. Two patients demonstrated complete clinical regression, two patients demonstrated greater than 80% partial clinical regression, two patients demonstrated less than 35% partial clinical regression, and one patient progressed. However, two patients developed new squamous cell carcinomas at uninvolved sites.<sup>4</sup>

There are currently multiple treatment options for

locally advanced basal cell carcinoma, including surgery, targeted therapy, and neoadjuvant therapy followed by surgery.<sup>4</sup> Surgery remains the mainstay of treatment for locally advanced basal cell carcinomas, with a much higher cure rate compared to the response rates of vismodegib.<sup>1</sup> However, there are limitations to surgery. For example, cases could be inappropriate for surgery due to compromise of function or cosmesis, multiple recurrences or low likelihood of surgical cure.<sup>5</sup> As in our case, surgery at the initial presentation would have sacrificed the patient's eye; therefore, neoadjuvant therapy was attempted to ideally shrink the tumor and spare the eye.

## Conclusion

Vismodegib may serve an important role in the future treatment of metastatic and locally advanced basal cell carcinoma. However, due to vismodegib's new and exciting development, there potentially may be cases of vismodegib use where surgery may have been indicated. Inappropriate use of vismodegib could potentially place the patient at increased risk without an increased benefit compared to surgical treatment.

Vismodegib's ideal treatment duration, long-term side effects, and cost effectiveness, as well as potential for causing resistance, residual skip lesions and squamous cell carcinoma remain unknown and warrant further investigation. These current limitations of vismodegib may discourage its future use.

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**Correspondence:** Madeline Tarrillion, DO; University Hospitals Case Medical Center, Department of Dermatology, 11100 Euclid Ave., LKS 5028, Cleveland, OH 44106; Ph: 216-844-5794; F: 216-844-8993; Madeline.tarrillion@uhhospitals.org

# Superficial Angiomyxoma: A Case Report

Elizabeth M. Aradine, DO,\* Albert E. Rivera, DO,\*\* Mark Teague, MD\*\*\*

\*Intern, Preliminary Medicine, St. Vincent Charity Medical Center, Cleveland, OH

\*\*Dermatologist and Mohs Surgeon, Southeastern Skin Cancer & Dermatology, Madison, AL

\*\*\*Dermatopathologist, Pathology Associates, Huntsville, AL

## Abstract

*Superficial angiomyxoma is a benign proliferation of highly vascular myxoid cells. Herein, we report a case of a solitary, superficial angiomyxoma of the nasal dorsum in a patient without Carney complex. In the literature, there are 28 reports of superficial angiomyxoma found on the head and neck. Two of the case reports describe lesions on the nasal dorsum, each treated with a different method. We present another case of superficial angiomyxoma on the nasal dorsum and compare our patient's treatment and outcome -- wide local excision with disease-free survival for 11 months at time of writing -- with the other reported cases.*

## Introduction

Superficial (or cutaneous) angiomyxoma, a benign proliferation of highly vascular myxoid cells, can appear as a solitary lesion or as multiple lesions associated with Carney complex.<sup>1-3,5</sup> Superficial angiomyxomas more commonly occur in men and have a predilection for the head, neck, and trunk.<sup>2,3</sup> The majority of superficial angiomyxomas (75%) do not have epithelial components, and these have a lower recurrence rate than those with epithelial components.<sup>2,3</sup> Current recommended treatment is wide local excision; however, it has a 20% to 30% local recurrence rate.<sup>3</sup> Superficial angiomyxomas are not to be confused with aggressive angiomyxomas, which are deeper myxomas with high vascular proliferation, more common occurrence in women and a predilection for the vulvar region.<sup>6,7</sup> Here, we present the case of a 55-year-old male with a solitary superficial angiomyxoma of the nasal dorsum without evidence of Carney complex. The patient was treated with wide local excision and remains disease free at 11 months.

## Case Report

### Presentation

A 55-year-old male presented to our clinic with a painless, enlarging papule on the left side of his nose. It had been growing for two years and was frequently irritated by his eyeglasses. Per his report, the lesion started as a "pimple" and had



Figure 1

enlarged over time. A second complaint was another large "mole," also on the left side of his nose, that had been present for years. This lesion had not changed in size in the past few years but was mildly painful and was also irritated by his eyeglasses.

Physical exam showed two flesh-colored to slightly pigmented papules on the left nasal root and left nasal side wall (Figure 1). The lesion clinically appeared as a benign dermal nevus.

### Differential

The clinical differential diagnosis of the patient's benign-appearing papule includes benign nevus and, less likely, basal cell carcinoma.

### Testing

The patient underwent a shave biopsy and shave removal of the respective lesions due to history and examination.

### Diagnosis

Pathology of the lesion revealed a multinodular growth of myxoid areas that contained scattered spindle and epithelioid cells (Figures 2, 3). Some scattered small blood vessels were seen but were not a predominant feature. Inflammatory cells such as lymphocytes, mast cells, and neutrophils were present with occasional multinucleate cells and minimal atypia. The mitotic activity was sparse. Immunohistochemistry stain was negative for S100, actin and calponin and positive for CD34. Although there was little development of the vascular component, the histologic findings were most compatible with a benign superficial angiomyxoma. (Of note, one differentiating factor between aggressive angiomyxomas and superficial angiomyxomas is that the former are desmin-positive on pathology staining.) The other lesion was found to be a benign nevus.

### Treatment

Recommended treatment was wide local excision, which the patient underwent without complication shortly after his visit. The patient has been disease-free, with no signs or symptoms of recurrence, for 11 months at the time of writing of this article.

## Discussion

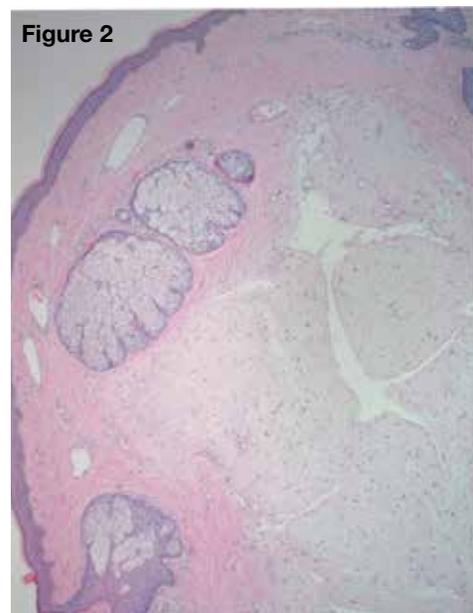


Figure 2

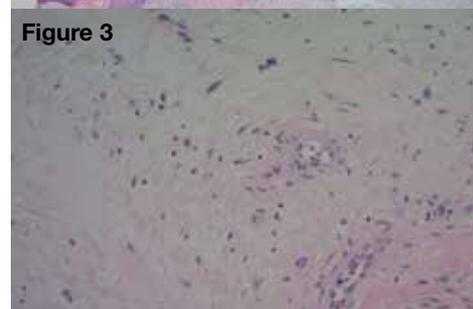


Figure 3

Figures 2 and 3. H&E, 40x/200x: Pathology showing multinodular growth of myxoid areas containing scattered spindle and epithelioid cells.

Our patient presented with a benign-appearing papule with the clinical differential diagnosis of benign nevus and, less likely, basal cell carcinoma. Reported clinical differential diagnoses considered in other cases of angiomyxomas on different locations of the body have included verruca vulgaris, lipoma, and tumor or lesion not specified.<sup>1,11,12</sup> The pathological differential diagnosis of our lesion includes neurothekeoma, myxoma, and plexiform fibrohistiocytic tumor. Other reports have given pathological differentials including, but not limited to, cutaneous myxoid cysts, focal cutaneous mucinosis, myxoid neurofibroma, and aggressive angiomyxoma.<sup>2,3</sup>

Wide excision of superficial angiomyxoma has been the historical treatment of choice and can be curative; however, this is not easily accomplished, as studies show the local recurrence rate is 20% to 30%.<sup>1-3,5</sup> Recurrence is typically dependent on depth of invasion, presence of epithelial components, and adequacy of lesion excision.<sup>1-3,7,8</sup> Most superficial angiomyxomas invade past the dermis and into subcutaneous tissue.<sup>2</sup> Increased depth of invasion is directly related to increased aggressiveness and recurrence in multiple tumors. While there are no studies directly looking at this relationship in the superficial angiomyxoma, it would be likely that the aggressiveness and recurrence of superficial angiomyxomas directly increase with depth as well; this could be a topic of further research. Research does indicate that lesions with presence of epithelial components have a higher tendency to recur, with a rate of 68% compared to 13% in lesions without epithelial components.<sup>2</sup> The median recurrence time of superficial angiomyxoma is 18 months;<sup>2</sup> however, lesions have recurred after up to 20 years.<sup>1,3</sup> For the aforementioned aggressive angiomyxomas, current recommended treatment is also wide local excision, but these lesions are more locally aggressive and have an increased recurrence rate of 36% to 72%.<sup>6,10</sup> Although uncommon, metastases from aggressive angiomyxomas have been reported.<sup>10</sup>

There are 28 reported cases of superficial angiomyxoma occurring in the head and neck region.<sup>9</sup> Two cases are reported with a superficial angiomyxoma in a location similar to ours. Each was treated with a different type of excision and resulted in different outcomes.<sup>7,8</sup> One report described a superficial angiomyxoma on the nasal dorsum treated with wide local excision.<sup>7</sup> It recurred multiple times in 26 years, with the longest disease-free interval at eight years. The latest treatment of that lesion was reported to be a wide local excision with a 0.5 cm margin. Inadequate excision was the presumed cause of previous recurrences, although margins were not reported from prior excisions. The patient remained disease-free two years post the latest excision. The other reported case of superficial angiomyxoma on the nasal dorsum was treated by Mohs surgery.<sup>8</sup> The patient was disease-free 18 months post excision. Both methods, wide local excision and Mohs, appear to be options for treatment of superficial angiomyxoma.

## Conclusion

While our patient and both of the comparative cases were relapse-free upon latest follow-up, extended follow-up is still required. Although wide local excision is currently the treatment of choice for superficial angiomyxomas, there are no studies defining the optimal margins of wide local excision for an acceptable cure rate. Since this is a relatively rare tumor, the determination of a sufficient margin is left to the physician's discretion. With its tissue-sparing benefits and potential lower risk of recurrence (providing less long-term morbidity from additional surgery as well as cost savings), Mohs micrographic surgery

could ultimately prove to be more appropriate. Nevertheless, the efficacy and recurrence need further study in trials. Although the low incidence of this lesion can make sufficient statistical power more difficult, it can be a worthwhile future investigation.

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**Correspondence:** Elizabeth M. Aradine, DO, 2351 E 22nd Street, Suite 342W, Cleveland, OH 44115; Ph: 216-861-6200; F: 216-363-2721; Elizabeth.aradine@gmail.com

# Syringoid Eccrine Carcinoma: A Case Report and Review of the Literature

Jill Salyards, DO,\* Daniel J Hogan, MD,\*\* Drazen M. Jukic, MD,\*\*\* Richard Miller, DO, FAOCD\*\*\*\*

\*Dermatology Resident, 2nd year, NSUCOM/Largo Medical Center, Largo, FL

\*\*Dermatologist, Bay Pines VA Healthcare System, Bay Pines, FL

\*\*\*Dermatopathologist, James A. Haley VA Healthcare System, Tampa, FL

\*\*\*\*Program Director, Dermatology Residency Program, NSUCOM/Largo Medical Center, Largo, FL

## Abstract

*Syringoid eccrine carcinoma is a rare sweat gland carcinoma that can be difficult to diagnose. The clinical and histologic appearance is often nonspecific. Therefore, immunohistochemistry is often helpful with making the diagnosis. We report a case of syringoid eccrine carcinoma of the scalp and review the current literature.*

## Introduction

Syringoid eccrine carcinoma (SEC) is a rare, malignant adnexal tumor that can be challenging to diagnose both clinically and histologically. Clinically, the tumor has a nonspecific appearance and can often resemble basal cell carcinoma. Histologically, differentiation from other benign and malignant tumors can be difficult. Immunohistochemistry can be helpful in helping differentiate SEC from other neoplasms and adenocarcinomas with skin metastases. We report a case of SEC that clinically presented and was treated as basal cell carcinoma and review the current literature.

## Case Report

A 67-year-old white male presented with a several-year history of an enlarging, tender lesion on the posterior scalp. Physical examination revealed a pink, pearly, well-demarcated papule with overlying telangiectasia measuring 7 mm x 5 mm in diameter (**Figure 1**). No detectable lymphadenopathy was present upon examination. The lesion was clinically suspicious for basal cell carcinoma and was scheduled for surgical excision. The lesion was excised with 4 mm margins and sent for histologic examination.

Examination of the hematoxylin-and-eosin (H&E) stained specimen showed a small, well-circumscribed neoplasm of ductal structures with an infiltrating growth pattern surrounded by a desmoplastic stroma (**Figures 2, 3**). The tumor extended into the reticular dermis. Scattered mitotic figures were present. No evidence of perineural invasion was seen in this case. The tumor extended to the lateral tissue edges. Immunohistochemical analysis was performed, and there was found to be CEA, EMA, CK7 and p63 positivity.

Due to the positive margins, the patient was sent to plastic surgery for frozen section procedure. The tumor was excised with clear margins, and no signs of recurrence were noted at one-month follow-up.

## Discussion

SEC is a rare type of sweat gland carcinoma originally described as basal cell carcinoma with eccrine differentiation (eccrine epithelioma) by

Freeman and Winkelmann in 1969.<sup>11</sup> There are various synonyms for and variations of this tumor, including syringomatous carcinoma, malignant syringoma, squamoid eccrine ductal carcinoma, sclerosing sweat duct carcinoma, sweat gland carcinoma with syringomatous features and, as previously mentioned, eccrine epithelioma.<sup>1,2</sup>

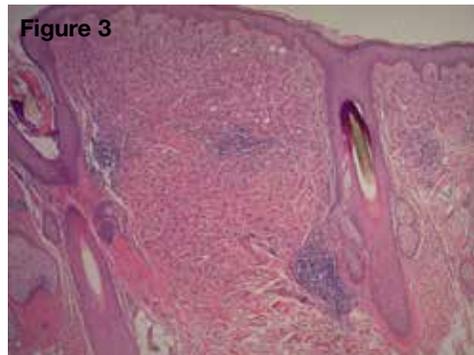
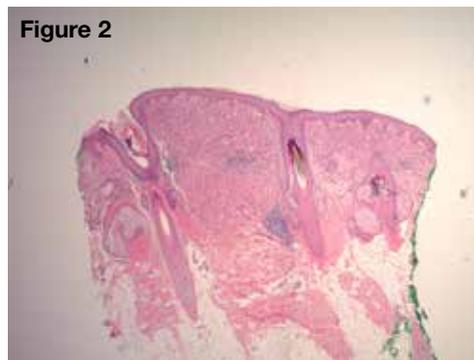
The clinical presentation of SEC is nonspecific and can vary, but most commonly the tumor presents as a solitary, firm nodule or plaque on the scalp that is sometimes painful. Ulceration is uncommon. SEC occurs mostly in the fifth and sixth decades of life and affects males and females equally. The tumor is slow-growing and locally aggressive with deep invasion. Multiple local recurrences are common, yet metastases are rare. Most reported cases of metastasis involve lymph nodes, with rare reports of metastasis to lung and bone.<sup>1,3,7,12</sup>

Histologically, SEC has a tadpole-like morphology composed of a basaloid cell infiltrate with ductal differentiation surrounded by a dense fibrous stroma. Small epithelial cells are present with hyperchromatic nuclei, pale cytoplasm and indistinct cell membranes arranged in narrow cords. The tumor is deeply invasive, often extending into the subcutaneous tissue and muscle. Cytologic atypia and mitotic activity are variable. Perineural invasion is common and likely contributes to the tendency of local recurrence.<sup>1,3,4</sup>

The immunohistochemistry of SEC tumors is nonspecific and variable. Simple epithelial cytokeratins (CKs 7, 8, 18, 19) are expressed by most tumor cells, and a small number express stratified epithelial cytokeratins. (CKs 5, 14).<sup>1,8</sup> Tumor cells also commonly express EMA and CEA and occasionally express S-100 protein. Studies also demonstrate that the majority of primary adnexal tumors strongly express p63, as in our case. Other antigens reported to be positive in SEC include Ber-EP4, ER and PR.<sup>1,3,6</sup>

SEC can be difficult to differentiate from a variety of other tumors including syringoma, basal cell carcinoma, microcystic adnexal carcinoma (MAC), primary cutaneous adenoid carcinoma (PCACC), and visceral adenocarcinoma with skin metastases.<sup>1-3</sup> Syringomas lack the cellularity, deep invasiveness and anaplasia that SEC demonstrates.<sup>3,5</sup> SEC differs from basal

cell carcinoma by the lack of retraction artifact, characteristic palisading arrangement, and by the presence of EMA and CEA positivity. Basal cell carcinoma rarely shows ductal differentiation as seen in SEC.<sup>1-3</sup> MAC displays eccrine and follicular differentiation and is composed of nests and strands of basaloid cells forming keratin-filled cysts, which are not present in SEC. SEC differs from PCACC in that it lacks the prominent cribriform pattern of tumor growth and mucin production demonstrated by PCACC. SEC and PCACC are similar immunohistochemically.<sup>1,2</sup> Tumor morphology and immunohistochemistry



distinguish SEC from skin metastases due to visceral adenocarcinomas, such as breast, lung and kidney. Immunohistochemical markers that can help differentiate these tumors from SEC include mammoglobin and gross cystic disease fluid protein for breast carcinoma, thyroid transcription factor 1 for lung carcinoma and CD10 and renal cell carcinoma marker for renal cell carcinoma.<sup>1</sup>

Surgical excision with clear margins is considered the treatment of choice for localized SEC. Mohs' micrographic surgery has been considered the method of choice for localized lesions if there are no "skip" areas or evidence of multi-focality.<sup>2,4,9</sup> In our case, Mohs' micrographic surgery was not an available option, and frozen section procedure was performed to ensure clear margins. Chemotherapy and radiation therapy have been used for metastatic sweat gland carcinomas with variable results.<sup>2,4</sup> As previously mentioned, local recurrence is common, and approximately 40% to 60% of reported cases had one or more local recurrences within six months to 30 years after treatment with standard wide local excision.<sup>7</sup>

## Conclusion

In conclusion, SEC can demonstrate variability in both clinical and histologic appearance. Immunohistochemistry, therefore, is crucial in differentiating SEC from other neoplasms. Due to the locally aggressive nature of the tumor, recurrence is common, though metastasis is rare. Excision with clear margins is the treatment of choice, and good results have been achieved by Mohs' micrographic surgery.

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**Correspondence:** Jill Salyards, DO;  
jillsalyards@gmail.com

# Segmental Neurofibromatosis: A Rare Case and Review of the Literature

Yuri Kim, DO,\* John Moesch, BA,\*\* Frank Don, DO,\*\*\* Stanley Skopit, DO, MSE, FAOCD,\*\*\*\* Francisco A. Kerdel, MD\*\*\*\*\*

\*Dermatology Resident, 2<sup>nd</sup> year, Larkin Community Hospital/NSU-COM, South Miami, FL

\*\*Medical Student, 3<sup>rd</sup> year, Philadelphia College of Osteopathic Medicine, Suwanee, GA

\*\*\*Dermatologist, Florida Academic Dermatology Center, Coral Gables, FL

\*\*\*\*Program Director, Dermatology Residency Program, Larkin Community Hospital/NSU-COM, South Miami, FL

\*\*\*\*\*Director of Inpatient Dermatology, Larkin Community Hospital/NSU-COM, South Miami, FL

## Abstract

*Segmental neurofibromatosis is a very rare subtype of the neurofibromatoses. Affected individuals have a segmental distribution of neurofibromas or pigmentary changes including café-au-lait macules or axillary freckling. It is an example of somatic mosaicism caused by a post-zygotic mutation in the NF-1 gene. Familial transmission and systemic complications are rare. We report a case of a 42-year-old female with no family history of neurofibromatosis diagnosed with segmental neurofibromatosis on her right neck and shoulder.*

## Introduction

Segmental neurofibromatosis (SN) is a rare subtype of the neurofibromatoses. The most recent literature reports only 150 documented cases.<sup>1</sup> The prevalence ranges from .0014% to .002%.<sup>2</sup> The first reported cases of segmental neurofibromatosis were published in 1931 by Gammel and in 1956 by Crowe et al.<sup>3</sup>

Due to the heterogeneous nature of NF, Riccardi created a classification system that divided NF into eight different subtypes (Table 1). SN became labeled neurofibromatosis type V and was defined as café-au-lait macules and/or axillary freckling, and/or neurofibromas distributed in a single unilateral segment of the body, without midline crossing, family history, or systemic involvement.<sup>3,4</sup> In 1987, Roth observed that the diverse clinical presentations of SN would not

fit into the rigid classification system created by Riccardi, and he therefore divided SN into four subtypes: true segmental, localized with deep involvement, hereditary, and bilateral.<sup>5</sup> Herein, we report a case of a patient with true segmental neurofibromatosis.

## Case Report

A 42-year-old female with a past medical history significant only for anxiety presented to our dermatology office complaining of “moles” on her right neck extending to her right shoulder. The patient stated that the bigger lesions had been there since birth, and approximately 10 years ago, smaller lesions had erupted in the same region. The patient denied any symptoms, including pruritus or pain. She denied any prior treatments. A complete review of systems was negative, including any visual, hearing, or neurological complications. The patient denied any family history of neurofibromatosis.

Physical examination showed multiple pink-brown, dome-shaped papules and nodules extending unilaterally from her right lower neck to her right shoulder, varying in size from 0.3 cm to 0.8 cm (Figures 1, 2). The patient did not have any signs of axillary freckling, café-au-lait macules, or Lisch nodules.

An excisional biopsy of her right shoulder was performed. Histologic examination showed a well-circumscribed nodule composed of delicate wavy fibrils of neural origin with elongated fibroblasts and some mucoid change in the stroma with a slightly irregular epidermis (Figures 3, 4), consistent with true segmental neurofibromatosis

transmitted to offspring in a familial pattern have been reported.<sup>1</sup> There have been two case reports of offspring affected with generalized NF with the history of one parent having NF.

The large majority of SN cases can be explained by a post-zygotic somatic mutation on the NF1 gene present on chromosome 17.<sup>7</sup> The somatic mutation occurs during late embryonic development and results in mosaicism. Mosaicism occurs when cells in the body are of more than one genotype. Somatic mosaicism is not transmitted to offspring because it does not affect gonadal cells. On the contrary, post-zygotic gonadal mosaicism occurs during the early embryonic period in cells that are not terminally differentiated.<sup>8,9</sup> Gonadal mosaicism is believed to be the origin of the rare cases of familial transmission that can result in offspring with generalized NF1. Interestingly, the risk of generalized NF1 transmission from a parent with SN has been found to be proportional to the percentage of body involvement in the parent.<sup>10</sup> Additional research needs to be undertaken to examine the relationship between more severe presentations of SN and gonadal mosaicism.



Figure 1



Figure 2

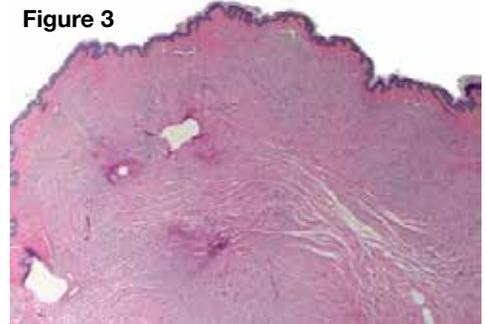


Figure 3

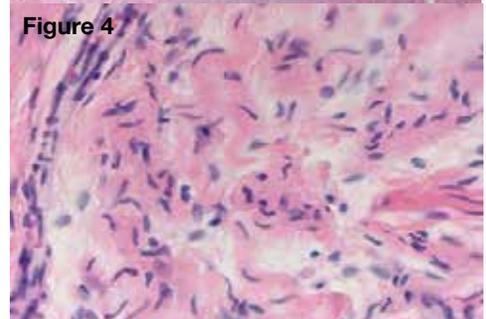


Figure 4

## Discussion

### Genetics

Segmental neurofibromatosis (SN) is a rare clinical subtype of the neurofibromatoses. While neurofibromatosis type 1 (NF1) is primarily inherited in an autosomal-dominant fashion, the majority of SN patients have no consistent pattern of genetic transmission. It is generally considered a non-inheritable disorder. A literature review of 82 cases of SN showed that 93% of patients had no family history.<sup>6</sup> However, exceptions to this rule exist, and nine cases of SN

## Clinical Presentation

The clinical presentation of SN is fairly standard between patients. However, rare presentations have been reported in the literature. The largest case review of SN was done by Hager in 1997.<sup>6</sup> He examined the clinical presentation of 82 patients with biopsy-proven SN. He found that the median age of onset was 28 years and that the incidence was higher in women (58%). Out of the 82 patients, 100% had neurofibromas, 26% had café-au-lait macules, and 10% had axillary freckling. Most neurofibromas were located unilaterally; however, five patients had bilateral neurofibromas. Most patients had only a single dermatome affected. Interestingly, recent case reports have documented patients with SN present on multiple dermatomes.<sup>10</sup> The cervical (38%), thoracic (40%), and lumbar (24%) dermatomes were the most commonly affected regions. Facial involvement is rare but has been reported in five cases.<sup>1</sup> Only 21% of patients had any additional systemic involvement. The most common systemic complaints in this study were painful neurofibromas (seven patients) and pruritic neurofibromas (four patients). Another clinical finding appreciated in SN patients is an increase in clinical severity during puberty and pregnancy.<sup>2</sup> The increase in severity during pregnancy is directly related to increased activity of progesterone receptors on NF1 tumors cells.<sup>2</sup>

The clinician should approach suspected SN as a phenotypic subtype of NF1 so as not to miss crucial physical findings more commonly present in generalized disease (NF1). The appearance of Lisch nodules in patients with SN is extremely rare. There has been one documented case of Lisch nodules in a patient originally diagnosed with SN.<sup>11</sup> While the exact significance of Lisch nodules in SN is unknown, the absence of Lisch nodules most likely lessens the risk of transmission to offspring.<sup>12</sup> Another clinical finding that needs to be examined in patients presenting with suspected SN is asymptomatic internal neurofibromas.<sup>5</sup> Patients with internal neurofibromas need further imaging, and depending on the results might need to be reclassified into another subtype of NF.<sup>5</sup> Sloan et al. suggests waiting until after puberty to discuss genetic counseling because the absence of Lisch nodules and internal neurofibromas becomes more significant to prognosis at that point, as they usually do not appear until this age.

## Association with Malignancy

Recent literature has shown that patients with SN have an increased risk of developing malignant tumors. Ten patients with both SN and malignancies have been reported to date. The incidence of malignancies in patients with SN is 5.3%, compared to the 7% life-time risk for cancer in documented in patients with NF1.<sup>12</sup> The two most common malignancies in patients with SN are malignant peripheral nerve sheath tumors and malignant melanoma.<sup>13</sup> Malignant peripheral nerve sheath tumors are also the most common malignancy in NF1 patients, revealing the close relationship between these two variants. Other tumors reported include

breast cancer, colon cancer, gastric cancer, lung cancer, and lymphoma. SN was diagnosed prior to cancer in half of the cases (5/10), while three of the 10 patients were diagnosed with SN after being diagnosed with cancer.<sup>13</sup> This demonstrates the importance of surveillance of SN patients for any suspicious cutaneous lesions or systemic symptoms.

## Differential Diagnoses

It is crucial to consider other skin disorders that may present clinically as dermatomal nodules. Infections, benign tumors, malignant tumors, and numerous other mucocutaneous conditions are known causes of dermatomal nodules (**Table 1**).<sup>6</sup> The primary infection that can present in a localized nodular distribution is syphilis. A recent case report examined an unusual presentation of secondary syphilis that followed a localized pattern as two granulation tissue-like nodules.<sup>18</sup> The benign tumors that can present similar to SN are linear syringocystadenoma papilliferum (SP) and trichoepithelioma. SP is an uncommon cutaneous adnexal tumor of uncertain etiology. Most cases of SP present as solitary lesions around the head and neck region. It often occurs in association with nevus sebaceous.<sup>19</sup> Trichoepithelioma is a facial hair follicle tumor that presents after puberty. It can appear similar to facial SN. On occasion it is associated with rare genetic conditions such as Brook-Spiegler syndrome and Cowden syndrome.<sup>20</sup> Other malignant tumors that resemble SN include basal cell carcinoma, squamous cell carcinoma, lymphoma, plasmacytoma, and cutaneous metastases. Other lesions that can mimic SN include sarcoidosis, pseudolymphoma, granuloma annulare, and rheumatic nodules. All of these differentials need to be excluded before the diagnosis of SN is made.

## Treatment

The management of cutaneous manifestations of SN can provide immeasurable benefit to the patient. Current treatments are limited, and there is presently no consensus on standard therapy.<sup>14</sup> Cutaneous neurofibromas and café-au-lait macules that are bothersome to the patient can be removed. The most common technique to remove neurofibromas is simple surgical excision.<sup>15</sup> This may be time-consuming and can result in pain and scarring. Laser ablation and electrocautery have been used on numerous smaller cutaneous neurofibromas; however, recurrences are possible.<sup>15</sup> Recent research has shown that CO2 laser treatment for neurofibromas can be effective and provide a high level of patient satisfaction and minimal pain. In one study using Lumenis 30c CO2 laser, more than 90% of the 106 patients in the study were pleased with the treatment. The drawback to the treatment was a 15% local infection rate and hypertrophic scarring.<sup>16</sup> Another study using a combination of shave excision and laser photothermocoagulation with 1,444 nm Nd:YAG laser showed excellent results. A seven-month follow-up showed no visible recurrence of neurofibromas or scars.<sup>14</sup> Similarly, treatment of neurofibromas with electrocautery

was effective. Electrocautery allows for quick treatment of numerous lesions with instant hemostasis and minimal thermal damage to surrounding tissue. In one study, all 97 patients treated with electrocautery were satisfied with the results and had minimal scarring.<sup>17</sup>

## Conclusion

SN is a rare and atypical variant of neurofibromatosis. Our case represents a typical clinical presentation of SN without generalization. The patient denied any familial history of neurofibromatosis or systemic complaints. The patient has one healthy offspring with no signs of neurofibromatosis. Close monitoring is vital for all patients with SN. Additionally, the cutaneous manifestations of SN can inflict emotional distress on patients. Counseling and cosmetic treatments should always be offered to patients. In addition to counseling, our patient had shave removal of the larger neurofibromas and electrocauterization of the smaller lesions with no complications.

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**Correspondence:** Yuri Kim, DO;  
[yurikim7@gmail.com](mailto:yurikim7@gmail.com)

# Shoulder Droop Following Excision of Malignant Melanoma on the Posterior Neck

William Scharpf, BS,\* Laura F. Sandoval, DO,\*\* Jonathan Stuart Crane, DO, FAOCD\*\*\*

\*Medical Student, 2<sup>nd</sup> year, Campbell University School of Osteopathic Medicine, Buies Creek, NC

\*\*Dermatology Resident, 2<sup>nd</sup> year, Sampson Regional Medical Center Dermatology Residency Program, Clinton, NC

\*\*\*Dermatologist, Dermone, Wilmington, NC; Program Director, Sampson Regional Medical Center Dermatology Residency Program, Clinton, NC

## Abstract

*A patient with malignant melanoma on his left posterior neck underwent a wide local excision in the left posterior triangle. Surgical procedures within this region can lead to severing or stressing of the spinal accessory nerve (SAN), which provides muscle innervation to the trapezius and sternocleidomastoid (SCM) muscles. Subsequent paralysis of these muscles will cause the shoulder on the affected side to droop downward. Chance of permanent disability is remarkably increased with failure to recognize signs and symptoms following surgery. While there are immediate treatments available for this condition, the best form of care remains prevention and proper awareness. We present a case of iatrogenic injury to the SAN as a result of a malignant melanoma excision in the left posterior triangle of the neck.*

## Introduction

In surgery of the skin, familiarity with anatomy such as important vessels and nerves is key. In cases of invasive melanoma and invasive squamous cell carcinoma that meet guidelines, sentinel lymph node biopsy may be recommended, possibly along with lymph node dissection. For skin cancers of the head or neck there is greater concern for metastases to nearby lymph nodes.<sup>1</sup> However, performing procedures in these areas can be associated with significant morbidities, the most common of which is shoulder dysfunction via injury of spinal accessory nerve.<sup>2</sup>

## Case Report

A 69-year-old male with a history of malignant melanoma presented for skin cancer surveillance and further evaluation of various skin lesions. At rest, the patient's left shoulder and clavicle were noticeably lower than those on the right side (**Figure 1**), with notable supraclavicular depressions due to trapezius and sternocleidomastoid atrophy (**Figure 2**). He had received a sentinel lymph node biopsy and a wide local excision to remove a malignant melanoma from his left posterior neck six years prior. Directly after the operation, the patient experienced "nerve issues and numbness" over the left side of his neck and shoulder. He has since had skin grafting performed by a plastic surgeon and was evaluated by a neurologist for the numbness.

## Discussion

The anatomical pathway of the SAN leaves it especially vulnerable to stress whenever operating on the lateral neck. The nerve crosses the jugular foramen beside cranial nerves IX and X before traveling obliquely downward to innervate the SCM and trapezius muscles.<sup>3</sup> Along this course, the SAN passes superficially through the posterior triangle, made up of the SCM muscle anteriorly, the trapezius muscle posteriorly and the middle third of the clavicle below.<sup>4</sup> The nerve's point of entry into this region lies in the middle of the posterior edge of the sternocleidomastoid muscle, at Erb's point. Here, branches of the cervical plexus disperse across the neck, providing

sensory and motor innervation to the back of the head and neck.<sup>5</sup> The only structure separating this delicate region from the skin is a layer of deep cervical fascia. Thus, an extreme level of caution is required during a radical neck dissection.

Other important landmarks to be cautious of when operating on the head and neck include branches of the facial nerve. Both the temporal and marginal mandibular branches of CNVII run superficially, putting them at greater risk for iatrogenic injury. The temporal nerve branch lies vulnerable due to its complex positioning amongst three layers of fascia in the temporal region, while the marginal mandibular nerve sits just beneath the shallow platysma muscle.<sup>6,7</sup>

Instances of shoulder droop as a result of SAN injury occur in up to 30% of patients who receive lateral neck dissections.<sup>8</sup> This could either be from a complete severing of the nerve or from partial injury followed by improper postoperative care. In the latter case, local ischemia from the initial damage leads to segmental demyelination of the remnant SAN.<sup>9</sup> If left unchecked, the nerve will eventually lose all function as if it were completely severed in the first place.

Patients with shoulder droop may also report a deep aching pain in their upper back and neck. This is most likely due to the straining of intact muscles, such as the rhomboids and levator scapulae, trying to compensate for change in the patient's posture.<sup>8</sup> Increased traction of the brachial plexus may result in similar irritation.<sup>10</sup>

In the event that the SAN is severed, early surgical reconstruction of the nerve has been shown to restore innervation.<sup>11</sup> For injuries without full ligation, aggressive physical therapy should be implemented to preserve trapezius and SCM function. Therefore, regular post-operative evaluations of the shoulder are crucial. Inability to recognize or react to the signs of accessory nerve injury is the largest complication of this condition. Quality management should include an appointment once a week for six weeks after surgery, followed by once a month thereafter.<sup>12</sup>

The best form of care, however, is preventing this condition altogether. A physician should be aware of the landmarks and possible complications



Figure 1. Left shoulder is appreciably lower than the right shoulder after injury to the spinal accessory nerve.



Figure 2. Supraclavicular depression due to trapezius and sternocleidomastoid atrophy.

involved with a neck dissection. When operating, physicians should locate the SAN and exercise caution so as not to cause such an unnecessary injury.

## Conclusion

In the example of this case study, the patient had already lost function in his left trapezius and SCM. Because the surgery was so long ago, it is unknown whether or not the SAN was fully cut initially, or simply injured but never acted upon. Ultimately, iatrogenic injury is avoidable, and caution should be used anytime a physician operates. When operating in the posterior triangle, the physician should be on the lookout for significant landmarks so as not to damage the accessory nerve. If an injury does occur, it should be managed with periodic inspection and physical therapy if applicable.

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**Correspondence:** Laura Sandoval, DO; 1099 Medical Center Dr., Wilmington, NC 28401; Ph: 910-251-9944; F: 910-763-4666; lsandovaldo10@gmail.com



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- Livability – one of best places to live
- Progressive Policy Institute - #4 America's high tech hot spots
- NerdWallet – top 10 US cities on the rise
- Google – digital capital of Alabama
- CNN Money – #7 great place to live and find a job in country
- NerdWallet – #3 best places for science, technology, engineering, math grads
- Family Circle – 10 best towns for families
- Policom – nation's top 20 economies
- Metro Magnets – fastest growing US cities
- Gallup - 4<sup>th</sup> most optimistic city in America
- Home of Redstone Arsenal
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