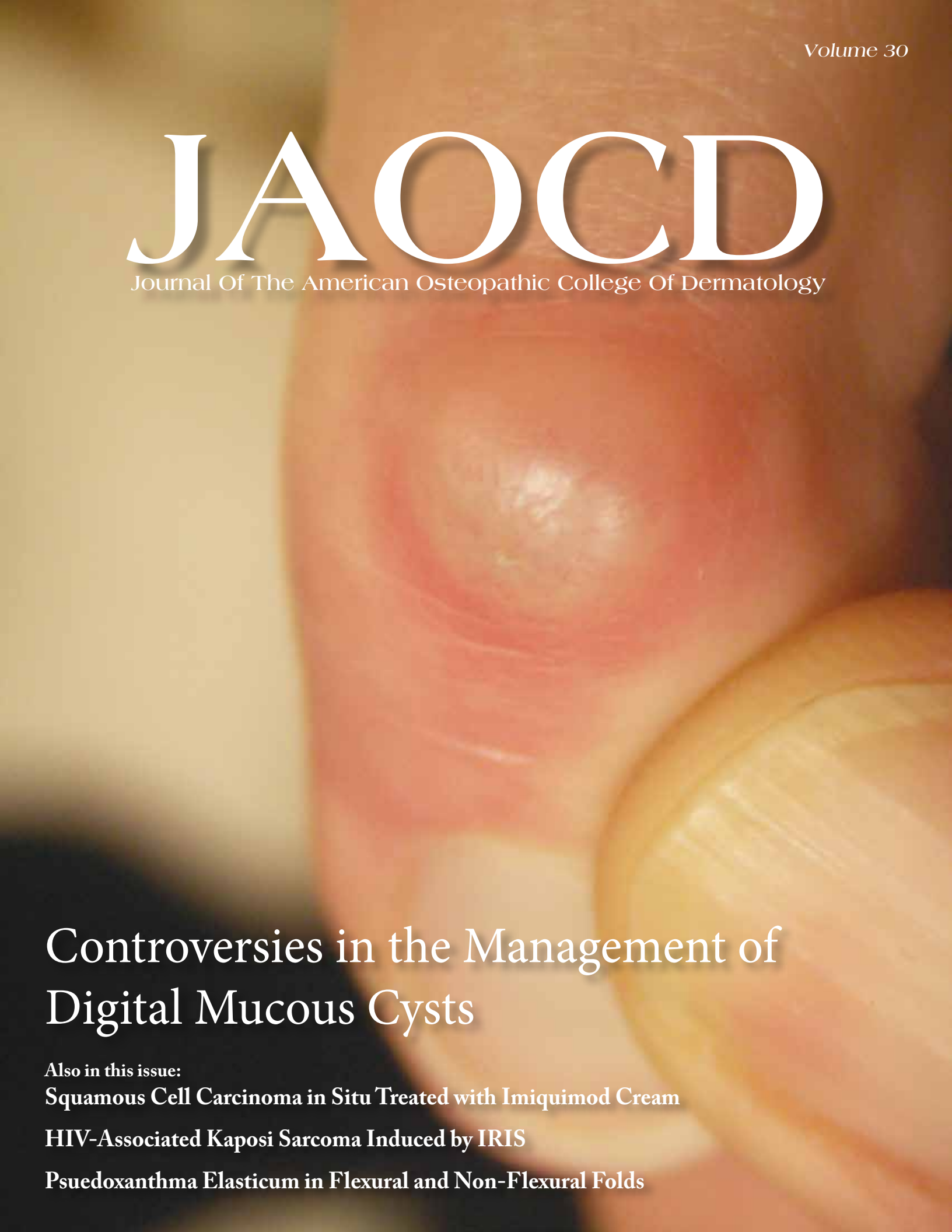
Volume 30

JAOCD

Journal Of The American Osteopathic College Of Dermatology



Controversies in the Management of Digital Mucous Cysts

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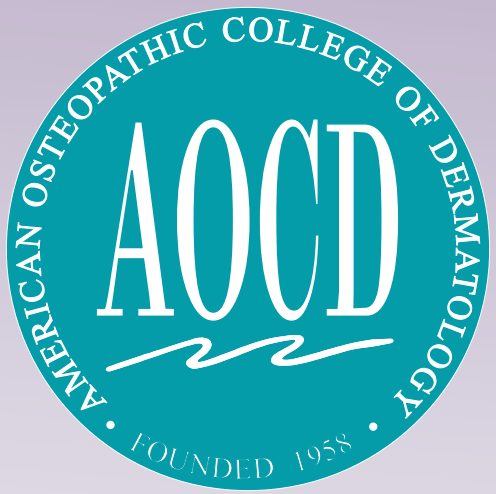
AMERICAN OSTEOPATHIC COLLEGE OF DERMATOLOGY
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JOURNAL OF THE
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AOCD • 2902 N. Baltimore St. • Kirksville, MO 63501
800-449-2623 • FAX: 660-627-2623 • www.aocd.org

Print and layout by: S&S Printing and Graphics LLC, 701 N. Marion St., Kirksville, MO 63501
Copy editing by: Julia Layton, Freelance Writing and Editing
Cover image courtesy of Davindra Singh, MD, AvantDerm, 45 Mill St., Toronto, ON

Journal of the American Osteopathic College of Dermatology

Table of Contents

Volume 30

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Letter from the Editor-in-Chief

Karthik Krishnamurthy, DO, FAOCD
Editor-in-Chief

Dear Readers,

Case reports are a cornerstone in the development and dissemination of information in medicine; however, in recent years, there has been a noticeable decrease in the amount of space available in journals to publish this type of manuscript. More space is being devoted to evidence-based articles and industry-driven data.

Wikipedia states:

"A case report is generally considered a type of anecdotal evidence. Given their intrinsic methodological limitations, including lack of statistical sampling, case reports are placed at the foot of the hierarchy of clinical evidence, together with case series. Nevertheless, case reports do have genuinely useful roles in medical research and evidence-based medicine. In particular, they have facilitated recognition of new diseases and adverse effects of treatments."

Some examples of discoveries directly resulting from case reports:

- The first heart transplant
- Thalidomide and teratogenicity
- Hallmark findings in HIV/AIDS

Our specialty is fortunate to still recognize the utility and importance of case reporting in presenting new findings, communicating novel therapeutic approaches, and creating networks to bridge knowledge gaps for rare conditions. While the JAOCD encourages review-based and practical-approach articles, there remains an unwavering commitment to reserve space for case reporting and literature review. We recognize their contributory role to the practice of medicine.

For more information, check out "A Practical Guide to Understanding a Case Report," PMID: 18312868.

Sincerely,
Karthik Krishnamurthy, DO, FAOCD
Editor in Chief, JAOCD
First Vice President, AOCD

Letter from the Executive Director

Marsha Wise
Executive Director, AOCD

Greetings, Everyone!
The year is quickly coming to an end, and it has been a very busy one. The main topic for this past year has been the Single GME Accreditation System. There were several resolutions regarding the Single GME Accreditation System, both for and against, at this year's AOA House of Delegates. Resolution 800, which was submitted by the AOA Board of Trustees, underwent numerous edits as a result of testimony in two different reference committees. It was edited again on the floor of the House on Saturday morning just before the vote. It was a highly emotional meeting for all parties, and debates were very spirited!

Some of the amended issues included:

1. The ability of AOA-trained and certified physicians to serve as program directors;
2. The maintenance of smaller, rural and community-based training programs;
3. The number of solely AOA-certified physicians serving as program directors in each specialty;
4. The number of osteopathic-identified GME programs and number of osteopathic-identified GME positions gained and lost;
5. The number of osteopathic residents taking osteopathic board-certification exams;
6. The status of recognition of osteopathic board certification being deemed equivalent by the ACGME; and
7. The importance of osteopathic board certification as a valid outcome benchmark of the quality of osteopathic residency programs.

With the passing of Resolution 800, the osteopathic profession will begin a journey into uncharted territory. It is our goal to get our membership informed, and we encourage everyone to monitor the AOA website for details and updates on the Single Accreditation System.

Save the Dates!

Our 2015 Spring Meeting will take place from April 23rd through 26th at the Ritz Carlton, Charlotte, in Charlotte, North Carolina. The Program Chair is Dr. Daniel Ladd.

The 2016 Spring Meeting will take place from March 30th through April 3rd at the Ritz Carlton New York, Battery Park, in New York, NY.

The 2017 Spring Meeting will take place from March 29th through April 2nd at the Ritz Carlton, Atlanta, in Atlanta, GA.

As always, if you have questions or concerns, please feel free to contact me (see "Contact Us" at AOCD.org), and I will be happy to assist you.

Sincerely,
Marsha Wise
Executive Director, American Osteopathic College of Dermatology

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Controversies in the Management of Digital Mucous Cysts

Ryan Bhagwandin, BS,* Jacqueline Thomas, DO, FAOCD,** Scott Greenberg, DO***

*Medical Student, 2nd Year, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL
**Assistant Professor, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL; Assistant Program Director, Dermatology Residency, NSU/Broward General Medical Center, Ft. Lauderdale, FL
***Clinical Assistant Professor, Orthopedic and Hand Surgery, Nova Southeastern University College of Osteopathic Medicine, Ft. Lauderdale, FL; Private Practice, Naples, FL

Abstract

Digital mucous cysts are benign, solitary, oval nodules that typically manifest on the dorsal aspect of the distal interphalangeal joint.[1-3] The management of digital mucous cysts differs between the fields of dermatology and orthopedic surgery. Dermatologists treat the cysts in a conservative manner that minimizes patient side effects and risk of scarring. Dermatologic treatment modalities such as sclerotherapy and cyst excision have cure rates over 80%. Alternatively, orthopedists' main preferences are more aggressive form of surgical treatment, which have remarkable cure rates. Orthopedic cure rates are over 90% when using techniques such as osteophyte debridement and synovectomy. Average recurrence rates for dermatologic treatment are 30%, while orthopedic recurrence rates are below 10%. There are no prevailing guidelines in the treatment of digital mucous cysts. Both treatment methodologies offer effective care to the patient; however, physician recommendations should be determined on a patient-by-patient basis.

History

Digital mucous cysts were first described in 1883 by Hyde, characterized as synovial lesions of the skin.[1,4,5] Hyde described these lesions as "pseudo-vesicles and bullae" and determined that they have a direct connection to the bursa of the synovium.[4,5] Orthopedic surgeons share this belief and aim to destroy the connection between the synovium and cyst.

Alternative names for digital mucous cysts are: myxoid cysts, synovial cysts, mucous cysts, and myxomatous cutaneous cysts.[1,3,6-8] These cysts commonly present as solitary, oval, smooth nodules near the distal interphalangeal joint.[1-3] Subungual mucous cysts and multiple mucous cysts are rare occurrences.[9-11]

Mucous cysts tend to affect individuals between 50 and 70 years old; presentation before age 50 is commonly associated with a previous major injury to that digit.[3,4] Women are affected more often than men, with a ratio of 5:1.[2,12] Although mucous cysts affect every race, they are especially prevalent among Caucasians.[4]

Anatomy and Physiology of Digital Mucous Cysts

Mucous cysts primarily arise from two main causes. The first is associated with the degeneration of the distal interphalangeal joint, and the second comes as a result of excessive hyaluronic acid produced from fibroblasts.[9,13] Mucous cysts associated with the former are the ganglion type, while the latter is the myxomatous type.[2,10] Although called mucous cysts, these nodules lack an epithelial lining and cyst wall, making them technically pseudocysts.[10,14,15]

Digital mucous cysts are located on the distal interphalangeal joint of fingers and toes (Figure 1). The position of the cyst is lateral to the midline on the dorsal side of the digit (Figure 2). This is due to the extensor tendon that runs along the midline of the finger, displacing any potential cyst that might occur there.[8] Mucoid cysts appear to have a definite border when examined externally, but histologically contain a steady transition from a fibroblast-dense area of the cyst to the typical collagenous tissue of the skin.[4] Microscopic examination of the cyst demonstrates increased fibroblast proliferation and a loose matrix.[4] Fibroblast proliferation leads to a rise in hyaluronic acid, which is one of the contributing factors to the formation of digital mucous cysts.[9,13]

Subungual mucous cysts are located beneath the nail plate, as the name implies, and can affect the nail matrix, causing several nail pathologies.[10] Interaction between digital mucous cysts and the nail matrix can lead to alteration of nail integrity, curvature, and color.[10] Treatment of the cyst can resolve complications of the nail matrix, leading to correction of nail deformities.[11] Failure to remove any attachment between the cyst and the connected joint capsule may further contribute to recurrence of the cyst.[16]

Irregular articular joint surfaces caused by osteophytes, as in arthritis, promote damage to the joint capsule, leading to points of weakness.[9,15] The deterioration of these points allows fluid to escape, potentially forming digital mucous cysts.[9,15] Failure to remove the osteophytes from the joint may further disrupt the joint capsule and lead to recurrence.[16]

Figure 1: Digital mucous cyst resting on nail matrix, resulting in nail-plate deformity.

Figure 2: Digital mucous cyst arising on the radial aspect of midline.

Therapeutic Approaches to Digital Mucous Cyst Management

The dermatologic and orthopedic surgery management philosophies aim to treat patients using different techniques. X-rays of the cyst are routinely taken in order to confirm the presence of osteophytes or other pathology.[17] Patients with digital mucous cysts who do not demonstrate any symptoms such as pain or major nail deformities may be advised to simply observe the cyst.[13] These types of patients routinely present to physicians for cosmetic purposes.

Dermatologic Approach to Therapy

Dermatologic management of a digital mucous cyst is primarily comprised of non-operative treatment methods. These therapies range from

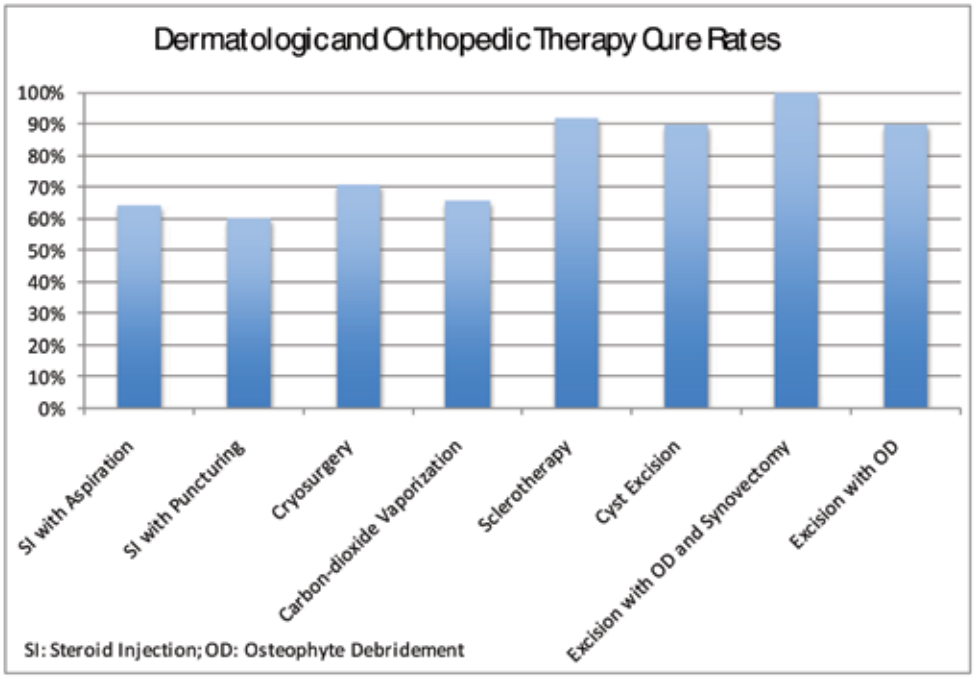

Table 1. Cure Rates of Dermatologic and Orthopedic Treatment of Digital Mucous Cysts

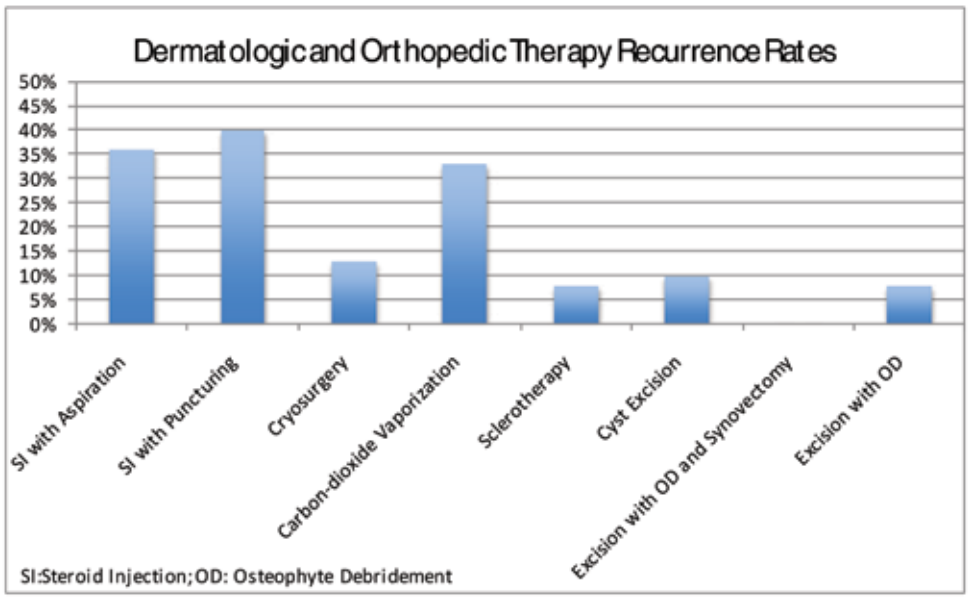

Table 2. Recurrence Rates of Dermatologic and Orthopedic Treatment of Digital Mucous Cysts

minor office procedures such as observation to complete excision of the cyst.[12,13] These techniques tend to be aesthetically pleasing and are associated with a low recurrence rate.[12] More aggressive management of digital mucous cysts increases the possibility of complications.[18]

Puncturing a mucous cyst is the starting point in various treatments. The initial step of puncturing involves determining the limits of the cyst through palpation.[19] Once the cyst is punctured and the contents aspirated, the cure rate is up to 72 percent after two to five treatments.[9] Validation of the digital mucous cyst diagnosis can be confirmed by the presence of clear, semi-viscous fluid removed from the cyst.[13] A majority of incompletely cured mucous cysts are downgraded to asymptomatic nodules.[20] After the contents of the cyst are vacated, the cyst can be injected with a steroid mixture.[13] Steroid injection is a common method of treatment used for myxomatous cutaneous cysts and is frequently paired with aspiration or cyst puncturing. The recommended initial solution for steroid injection contains 0.2 mL of 1% lidocaine and 0.2 mL of triamcinolone acetonide.[13] Triamcinolone is used to suppress fibroblast secretion, one of the main causes of digital mucous cysts.[4] Hyaluronidase has been injected in the cyst and is thought to chemically remove the contents, although it has been noted to be unsuccessful in some studies.[4] Dodge et al. reported that 64 percent of cysts were cured by either aspiration or decapping combined with a local steroid injection.[21] The remaining 36 percent of cysts recurred within four years.[21] A 2003 study by Rizzo and Beckenbaugh found that 48 out of 80 patients treated with multiple cyst punctures and injected with 1 ml of 1% lidocaine experienced successful regression.[22] The remaining 32 patients had the cyst reccur.[22] Decreased mobility of the joint and infection are complications accompanying steroid injection with aspiration or multiple punctures.[22]

Another therapy used to treat digital mucous cysts is cryosurgery. The cyst roof is opened and drained, and liquid nitrogen is then applied directly into the cyst cavity.[13] This allows for liquid nitrogen to be applied directly into the cyst.[13] A double cycle of quick-freeze, slow-thaw is proposed in order to increase the effectiveness of the treatment, since single freeze-thaw cycles have been associated with higher rates of recurrence.[23] The cure rates of cryosurgery range from 56 percent to 86 percent.[9] The rate of recurrence ranges from 10 percent to 15 percent.[13] Complications of cryosurgery are relatively minor, including hemorrhagic blister formation and discomfort.[24]

An increasingly popular therapy for the treatment of digital mucous cysts is carbon-dioxide vaporization under a digital block at a power of 5 watts to 10 watts.[25] Once punctured, the contents are squeezed out, yielding a clear, jelly-like liquid. Next, the cyst is completely vaporized using the carbon-dioxide laser.[25] The cyst is treated with hydrogen peroxide and then reexamined to ensure no traces of the cyst are left behind.[25] Caution is exercised in order to not damage the nail matrix, which could potentially lead to nail deformities.[25] In 1999, a study by Karrer demonstrated that 66 percent of patients were cured by carbon-dioxide laser vaporization. Two patients had the cyst recur, one at three weeks and the other at 11 months, after therapeutic treatment.[25] Karrer also noted no complications from the carbon-dioxide vaporization.[25] However, scarring, superficial erosion, and infection can occur postoperatively.[26] The rate of bacterial infection with conventional lasers is extremely low, between 0.5 percent and 4.5 percent, while fractional laser vaporization has a reported infection rate of 0.1 percent.[26]

Sclerotherapy is also used to treat digital mucous cysts. Sclerosants are detergents, chemical agents, and osmotic agents that disrupt the cellular membrane.[27] Before the cyst is injected with the sclerosant agent, the cyst is aspirated to remove mucinous contents.[27] Polidocanol is a detergent used as a sclerosant associated with positive aesthetic outcomes and low risk

of complications.[27] A study by Cordoba in 2008 used polidocanol as the sclerosant and successfully treated six digital mucous cysts with no recurrences.[27] Sodium tetradecyl, a similar sclerosant, has a cure rate of nearly 92 percent after an average of two treatments.[28] Sclerotherapy using sodium tetradecyl has an 8 percent recurrence rate.[28] Complications from sclerotherapy are inflammation, superficial necrosis, edema, and pain.[27,28]

A more aggressive method used is a simple excision of the cyst with surgical closure. Although this technique produces outcomes that are aesthetically pleasing, it is highly associated with recurrence of the cyst.[13,29] A U-shaped rotational flap is created to encompass the cyst, although in the presence of multiple cysts the location of the flap is based upon the largest cyst.[13,15] The cyst is then incised, the contents are extracted, and the cyst is finally curetted.[15] The flap can be left to heal on its own or sutured into place.[13,15] Lawrence et al. demonstrated a cure rate of nearly 90 percent in fingers and 33 percent in toes.[15] The rate of recurrence in this study was less than 10 percent in fingers and 66 percent in toes.[15] Importantly, there was no skin excision or osteophyte removal during this process.[15] This procedure has been limited to few complications such as pain, infection, and limited joint movement.[15]

According to Lawrence, raising a flap to include tissue of the cyst and distal interphalangeal will result in scarring.[15] The scar will seal the joint and prevent synovial leakage that may have contributed to the cyst.[15] A major distinction between dermatologic and orthopedic surgical techniques is the contribution of osteophytes to the recurrence of the digital mucous cyst. This discrepancy is the foundation of orthopedic management for digital mucous cysts.

Orthopedic Approach to Therapy

The orthopedic management of digital mucous cysts consists of more aggressive techniques of treatment. While dermatologists opt for less-invasive therapy and have a variety of treatment methods, orthopedic surgeons follow a stricter protocol. The approach of orthopedic surgeons increases the chance for post-operative complications but is correlated with an extraordinary success rate.[9] Osteoarthritis is particularly associated with the prevalence of digital mucous cysts, with up to a 78 percent occurrence.[4,30-32]

The most conventional treatment among those of the orthopedic field is mucous-cyst excision and debridement of osteophytes in the distal interphalangeal joint.[33] This therapy is very successful, with over a 90 percent cure rate.[33] The recurrence rate is 3 percent to 12 percent for cyst and osteophyte excision.[3] One approach described by Shin and Jupiter calls for an extended dorsal flap to help in the removal of larger cysts.[33] In this process, the cyst stalk is excised along with the dorsal capsule and synovium.[33] Dorsal osteophytes are also removed to help prevent recurrence of the cyst.[33] The triad of skin excision, synovectomy, and debridement of osteophytes of the distal interphalangeal joint leads to a 100 percent cure rate with no recurrences of the mucous cyst.[8] Complications include infection, nail deformity, swelling, and damage to the extensor tendon.[3,9,13]

An elliptical incision is commonly made when excising the mucous cyst and its components.[31] Although in many cases the scar heals well and no skin graft is needed, a larger cyst may require a graft or flap.

Discussion

The dermatologic and orthopedic approaches vary in their methodology but have the same goal. Table 1 illustrates the cure rates of dermatologic and orthopedic treatment. The dermatologic management of digital mucous cysts begins with less-invasive treatments such as puncturing, aspiration and steroid injection.

Puncturing and aspirating the cyst has been associated with high recurrence rates and a cure rate of over 70 percent. Recurrence rates of dermatologic and orthopedic treatments can be found in Table 2. Other beneficial and aesthetically pleasing treatments are carbon-dioxide vaporization and cryosurgery. Both therapies are recommended after failure of the cyst to respond to other less-aggressive treatment modalities. Sclerotherapy also displayed impressive cure rates, with over 90% of patients being cured, as shown in Table 1. Steroid injection of the mucous cyst displayed less than an ideal cure rate of 60 percent, even after multiple injections. Another limitation to this treatment is the lack of a standard steroid used. There are many options, each with its own benefit, though the absence of a definitive steroid may lead to mismanaged treatment. The therapy with the top cure rate is surgical excision along with osteophyte debridement and synovectomy. This technique also provided patients with a zero percent recurrence rate, as depicted in Table 2. Although this method has the best cure rate, it does not come without risks. By performing surgery, the potential for nail deformities, post-operative pain, and limited post-operative functional use of the joint is increased.[12] Once the less-intrusive alternatives have been unsuccessful, cyst excision along with osteophyte debridement is recommended to treat the patient. Overall, the average orthopedic cure rate is 95 percent, compared to the average dermatologic cure rate of 73 percent.

The preference of treatment for the patient can vary upon many factors. The cost of treatment can significantly impact the choice the patient makes. Another major factor in deciding among treatment options is the likelihood of morbidity after the procedure.

Conclusion

The digital mucous cyst is a prevalent condition with a controversial treatment profile. While the methods of therapy have a common goal, the routes to achieving that objective differ in degree of destruction and complication. While both the orthopedic approach and the dermatologic approach are acceptable options for care, specific points should be considered and reviewed with the patient during the decision-making process. Both approaches have benefits and drawbacks, different levels of intensity of involvement of care, different costs, and different prognoses. Orthopedic surgeons have documented high cure rates with surgical excision and osteophyte debridement. The risk for post-surgical complications are increased, and the procedures are more involved, but the prognosis is improved. The dermatologic perspective leads to an aesthetically pleasing result with low risk of complications and less intensity of involved procedures, but with a potentially worse prognosis. All treatments should be carefully deliberated upon before a selection is made. There is no standard treatment recommended to patients, allowing for a multi-disciplinary approach to patient care with dermatology, orthopedic and hand surgery for both initial and later management. Patient discussion of these concepts will allow for arrival at the best decision for each patient, with realistic expectations and no misunderstandings.

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Correspondence: Jacqueline Thomas, DO; jacqui.thomas@comcast.net

An Atypical Presentation of Squamous Cell Carcinoma in Situ Treated Successfully with Imiquimod Cream

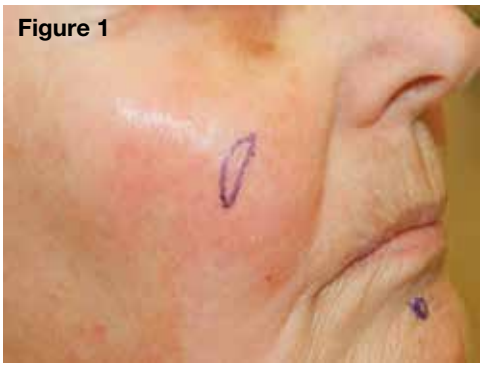
Raymond R. Knisley, DO,* Angelo A. Petropolis, MD,** Vernon T. Mackey, DO***

*Dermatology Resident, Third Year, Midwestern University/Advanced Desert Dermatology, Peoria, AZ
**Chief of Dermatology, Sierra Vista Regional Healthcare, Sierra Vista, AZ
***Residency Program Director, Advanced Desert Dermatology/Midwestern University, Peoria, AZ

Abstract

Squamous cell carcinoma in situ (SCCIS), also known as Bowen disease, is a histologic diagnosis.[1] It is the earliest, non-invasive form of squamous cell carcinoma (SCC). "In situ" indicates that the cancer cells are confined only to the epidermis and have not invaded the dermis.[2,3] If untreated, SCCIS can sometimes progress to an invasive squamous cell carcinoma.[4] Herein, we describe a patient with an unusual presentation of SCCIS, treated successfully with imiquimod 5% cream applied in multiple short bursts over a five-month time frame.

Figure 1

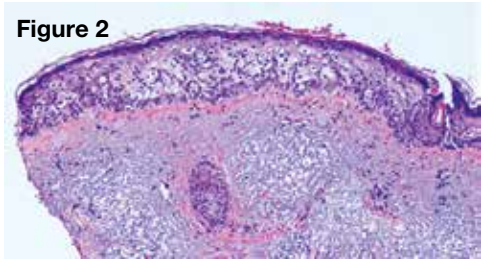


Case Report

An 84-year-old Caucasian woman presented with a red cheek of 10 years' duration. She stated that she had been applying topical triamcinolone 0.1% cream on the area for three to four weeks without change. On exam, she had a 6.0 cm x 6.0 cm erythematous, indurated, non-scaling, smooth plaque involving her entire right cheek from the lower eyelid to the nasolabial fold. There was a profound difference in skin texture when compared to her left cheek. Her left cheek appeared consistent with her age, while her right cheek was pristine, wrinkle free, shiny and red (Figure 1). Our differential diagnosis included a depositional disorder such as amyloidosis, a granulomatous process to include granuloma faciale, or one of the lymphocytic infiltrative disorders of the skin.

An incisional biopsy was taken from the central portion of the erythematous plaque. It showed hyperkeratosis, parakeratosis and acanthosis with full-thickness keratinocytic atypia consistent with squamous cell carcinoma in situ (SCCIS) (Figure 2). Since the morphology was atypical for SCCIS, four additional scouting punch biopsies were taken from the periphery of the erythema for confirmation and to evaluate the extent of

Figure 2



involvement. These too revealed SCCIS.

After discussing the diagnosis with the patient, she was presented with treatment options to include Mohs micrographic surgery (MMS) versus radiation therapy. If she opted for MMS, the defect would be rather large and quite challenging to repair without a large reconstructive flap or a skin graft, which would likely result in a poor cosmetic outcome. She declined radiation therapy due to the potential side effects of xerostomia and possible dental problems as well as her concern over the proximity to her eye. A third option was offered: to treat the lesion topically with either imiquimod or 5-fluorourocil. It was discussed with the patient that both imiquimod and topical 5-fluorouracil are off-label in the treatment of SCCIS; we opted to treat her with imiquimod 5% cream.

In anticipation of an exaggerated response, she began treatment with imiquimod 5% cream two nights per week with a plan to adjust application frequency based on her response and tolerance. The patient returned to the clinic five weeks later with an anticipated brisk, erythematous, crusted eruption. She was instructed to stop applications for four weeks, after which time we planned to restart her at two nights per week. At her follow-up appointment, her face had healed well, and she only had an erythematous patch in the treatment field. She restarted applications two nights per week in six-week intervals with a four-week break between cycles. With each cycle, her response became less intense until the point where she had only a minimal response. At this point, she had completed four six-week cycles. She was instructed to stop all applications to allow the area to heal, anticipating re-biopsy of the area to see if the treatment was successful. She returned in six weeks. Clinically, her right cheek had mild erythema with decreased induration and decreased fullness. Three additional scouting punch biopsies were taken from the center and periphery of the treatment area. All three biopsies were free of tumor without any epidermal atypia. She was free of disease at her six-month follow-up.

Figure 3

Discussion

Squamous cell carcinoma in situ (SCCIS), also known as Bowen disease, is a histologic diagnosis.[1] It is the earliest, non-invasive form of squamous cell carcinoma (SCC). "In situ" denotes that the cancer cells are confined only to the epidermis and have not invaded the dermis.[2,3] Like most other skin cancers, the major risk factor is excessive sun exposure, though arsenic exposure and human papilloma virus (HPV) are also risk factors.[3] If untreated, SCCIS can sometimes progress to an invasive squamous cell carcinoma.[4]

Clinically, SCCIS usually appears as asymptomatic, reddish, scaly patches that trend toward centrifugal spreading.[3] The epidermis may become atrophic or hyperkeratotic, and a cutaneous horn may develop over the lesion.[2] Our patient's SCCIS, however, did not present as such. The induration and rosy glow on her cheek may have been from underlying inflammation and edema, but the lack of scale and actinic damage typically associated with SCCIS were lacking. To our knowledge, this is the first report of a patient presenting with SCCIS in this manner.

Histologically, SCCIS shows atypical keratinocytes with hyperchromatic nuclei, nuclear pleomorphism, disordered maturation, multiple apoptotic keratinocytes, loss of the granular layer, parakeratosis and increased numbers of mitotic figures.[2-4] The epidermis may show a "wind-blown" appearance of the abnormal keratinocytes caused by loss of orderly maturation.[3] One may also see extension of the atypical cells down hair follicles. In early SCCIS, atypical keratinocytes are confined to the basal and suprabasal layers of the lower one third of the epidermis. The follicular structure is uninvolved. As lesions progress, atypical keratinocytes extend into the upper two thirds of the epidermis. Buds of keratinocytes in

the upper papillary dermis are also commonly found. Most pathologists define SCCIS at the point when atypical keratinocytes extend to more than two thirds of the full thickness of the epidermis and involve the epithelia of the hair follicle.[1]

Imiquimod, a nucleoside analogue of the imidazoquinoline family, is a topical immune-response modifier. It enhances both the innate and acquired immune responses, in particular the cell-mediated immune pathway.[5] The major biologic actions of imiquimod are thought to be mediated through agonistic activity on toll-like receptors (TLR) 7 and 8 and, simultaneously, activation of nuclear factor-kappa B (NF-kappa B). As a result of this activity, the induction of pro-inflammatory cytokines, chemokines and other mediators including IFN-α, IL-1, -6, -8, -10, -12, and TNF-α, leads to activation of antigen-presenting cells and other components of innate immunity.[5,6] This activity also stimulates natural killer cells and the proliferation of B-cells. In addition, it activates Langerhans cells, the key antigen-presenting cell in the skin, and promotes their migration to the regional lymph nodes. Imiquimod stimulates TH-1 cells to produce IFN-γ, which in turn can activate cytotoxic T lymphocytes' mounting of a profound T-helper (Th1)-weighted anti-tumoral cellular immune response.[6,7] Several secondary effects on the molecular and cellular level may also be explained, at least in part, by the activation of NF-kappa B. Furthermore, independent of TLR-7 and TLR-8, imiquimod appears to interfere with adenosine-receptor signaling pathways, and the compound causes receptor-independent reduction of adenylyl cyclase activity. This unique mechanism may augment the pro-inflammatory activity of the compound through suppression of a negative regulatory feedback mechanism that normally limits inflammatory responses. Finally, imiquimod induces apoptosis of tumor cells at higher concentrations. The pro-apoptotic activity of imiquimod involves caspase activation and appears to depend on B cell lymphoma/leukemia (BCL)-2 protein.[7] Imiquimod cream is only indicated for the topical treatment of clinically typical, non-hyperkeratotic, non-hypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults; biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults with a maximum tumor diameter of 2.0 cm on the trunk, neck, or extremities (excluding hands and feet) only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured; and external genital and perianal warts/condyloma acuminata in patients 12 years of age or older.[8]

SCCIS is a precursor to invasive squamous cell carcinoma. Therefore, it should be treated before invasive cancer develops. Treatment can involve both surgical and nonsurgical methods. Many articles describe the use of surgical excision, electrodessication and curettage, cryotherapy, 5-fluorouracil, imiquimod, radiation, photodynamic therapy, and lasers.[9] Although imiquimod is off-label for this purpose, there are reports of its successful use in treating SCCIS. Patel et al. performed a placebo-controlled trial of 15 patients and showed clearance in 11 of the 15 lesions versus zero in the placebo-controlled group.[2] Schroeder et al. and Cook-Bolden et al. also demonstrated complete clearance of SCCIS of the penis with imiquimod.[10,11] McKenzie et al. found it to be a successful treatment in 14 of 15 SCCISs of the lower limbs.[12] Furthermore, Smith et al. demonstrated successful use in combination with a COX inhibitor in the treatment of SCCIS in immunosuppressed patients.[13] Finally, there is also a report of successful treatment of SCCIS with a combination of imiquimod, 5-fluorouracil and tazarotene to the dorsal hands.[14]

Imiquimod 5% cream was the best option for our patient because we were able to tailor her treatment according to her response to and tolerance of the medication. It worked well to rid her of the condition.

There are still many unanswered questions, though. Our patient's clinical presentation was unusual, and perhaps imiquimod was more effective in our patient owing to enhanced penetration from decreased keratinization. Although additional, blinded studies with larger sample sizes are needed, imiquimod may be another treatment option for SCCIS when surgery or radiation therapy are not optimal choices.

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Correspondence: Raymond Knisley, DO; rayknisley@yahoo.com

HIV-Associated Kaposi Sarcoma Induced by Immune Reconstitution Inflammatory Syndrome Following Antiretroviral Therapy: A Case Report and Review

Marisa Wolff, DO,* Ali Banki, DO,** Kenneth P. Abriola, MD,*** Donna Aiudi, MD,**** Charles Gropper, MD,***** Cindy Hoffman, DO, FAOCD******

*PGY-2 Resident, St. Barnabas Hospital Dermatology Residency, Bronx, NY
**Private Practitioner, Ali Banki D.O., P.C., Glastonbury, CT
***Private Practitioner, Connecticut Health Care Group LLC, Glastonbury, CT
****Private Practitioner, Dermatologist, Glastonbury, CT
*****Chief of Dermatology, St. Barnabas Hospital, Bronx, NY; Associate Professor, Mount Sinai School of Medicine, Bronx, NY
******Program Director, St. Barnabas Hospital Dermatology Residency, Bronx, NY

Abstract

Classically, Kaposi sarcoma (KS) has been implicated as an HIV/AIDS-defining illness, presenting in patients with low CD4 counts and high viral loads. We present a case of an HIV-seropositive patient on antiretroviral therapy who developed KS lesions in the setting of an undetectable HIV-viral load and high CD4 T-cell count secondary to a paradoxical phenomenon known as immune reconstitution inflammatory syndrome (IRIS), in which lesions develop in parallel with an improved immune status. We will review the pathogenesis, diagnostic criteria and consequences of IRIS-induced HIV-KS following antiretroviral therapy.

Case Report

A 45-year-old, HIV-seropositive male presented to a private practice clinic complaining of a lesion on his left back, which had been enlarging over the course of one month. He also noted new lesions on the bilateral dorsal hands that had also developed over the course of a month. He denied pain, pruritus, burning, or bleeding of the lesions. Additional review of systems was otherwise negative. Review of medical history was significant for starting HAART approximately nine months prior to noticing the skin lesions. His viral load had been undetectable since beginning HAART, and his most recent CD4 count was reported as 704 cells/mm^3, an increase from his pre-HAART CD4 count of 658 cells/mm^3. History was additionally notable for same-sex encounters (MSM) and prior sexually transmitted disease, including treated syphilis and inactive genital herpes.

Physical examination revealed a solitary, well-demarcated pink nodule with overlying fine white scale on the left aspect of the back (Figure 1). On his bilateral dorsal hands were discrete, 1 cm, pink-to-violaceous, round flat-topped plaques with overlying fine white scale (Figure 2). Provisional diagnoses for the scapular lesion included: dermatofibroma, hypertrophic scar, dermal nevus, prurigo nodularis, basal cell carcinoma, Merkel cell carcinoma, adnexal neoplasms, Spitz nevus, dermatofibrosarcoma protuberans, atypical fibroxanthoma, lymphomatoid papulosis, pyogenic granuloma, bacillary angiomatosis, B cell lymphoma and Kaposi sarcoma. The differential diagnosis for the dorsal hand lesions included: granuloma annulare, annular lichen planus, Kaposi sarcoma, sarcoidosis, erythema elevatum diutinum, deep erythema annulare centrifugum, subacute cutaneous lupus erythematosus, and pseudolymphoma.

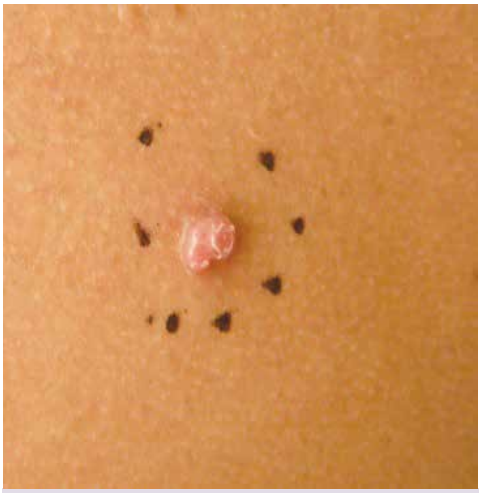

Figure 1: Solitary, well-demarcated, pink nodule with overlying fine white scale on the left back.

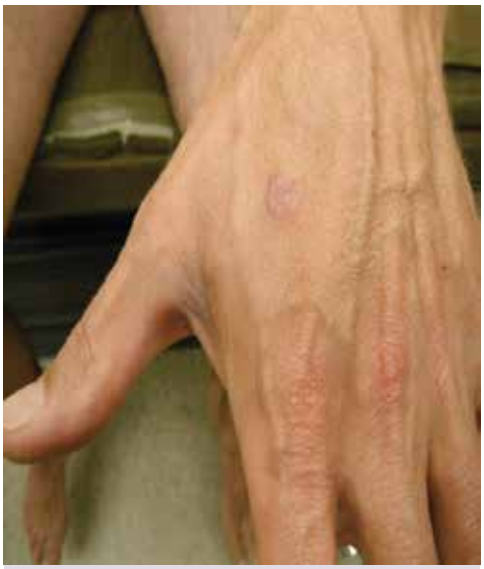

Figure 2: Discrete, 1 cm, pink-to-violaceous, round flat-topped plaques with overlying fine white scale on left dorsal hand.

A shave biopsy was performed on the lesions on the left back and left dorsal hand (Figures 3, 4). Both lesions shared similar histopathologic characteristics, with microscopic evaluation showing an intra-dermal, dense nodule composed of interweaving fascicles of spindle cells containing red blood cells. At the periphery of the nodules were granulation tissue, characterized by widely dilated blood vessels, a markedly edematous stroma, and a nuclear infiltrate containing plasma cells and siderophages (Figure 3). Immunostaining was positive for CD34 (Figure 4) and HHV8, highlighting hematopoietic origin of spindled cells and confirming the

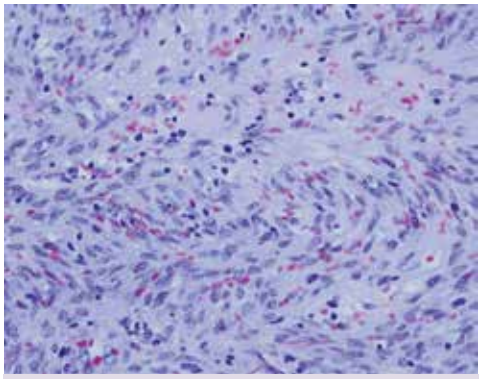

Figure 3: Lesion on back. H&E at 400x demonstrating intra-dermal dense nodule composed of interweaving fascicles of spindle cells containing red blood cells.

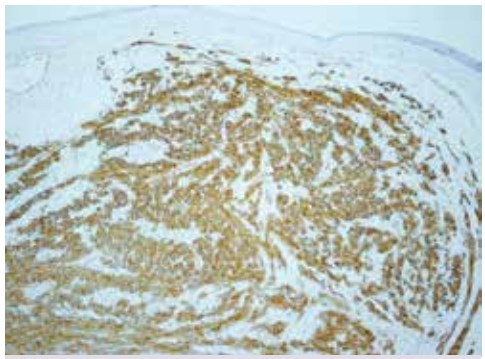

Figure 4: Lesion on dorsal hand. Immunostaining at 100X. CD34 positivity highlighting hematopoietic origin of spindled cells

diagnosis of KS, respectively.

Our patient was sent to oncology for further evaluation, with resultant laboratory studies and CT imaging negative for visceral disease. Since the lesions were limited to the skin, our patient elected to treat them locally with the vascular-specific pulse dye laser (585 nm) as an adjunct to continuing HAART. PDL was performed on lesions on his back and dorsal hands with the following parameters: 3 ms pulse duration, 13 joules/cm^2 fluence, and 7 mm spot size. Our patient tolerated the procedure well and has remained clinically stable with undetectable viral load and excellent CD4 count. The lesion on the back has remained quiescent after one treatment, and he continues to receive laser therapy to the dorsum of the hands.

Discussion

Kaposi sarcoma (KS) is an angioproliferative tumor capable of affecting the skin, lymph nodes or viscera. There are four subtypes of KS: classic, African-endemic, HIV/AIDS-associated, and iatrogenic/immunosuppression-related. These subtypes share many common features, including history of human herpes virus 8 (HHV8) expression within lymphatic and vascular endothelial cells as well as a variable clinical presentation ranging from localized to disseminated mucocutaneous and/or visceral disease. Phenotypic expression of HHV8 within KS lesions is due to a complex multi-factorial relationship between several factors including HHV8 gene expression, HIV status, immune impairment, cytokine dysregulation and other yet-to-be identified factors.[3] Histological features of KS do not vary between clinical subtypes, but they do vary by stage of lesion. Clinically, lesions tend to vary in severity but are typically erythematous-to-violaceous papulonodules that enlarge with time.

The most common presentation of KS is the HIV-related subtype. Historically, HIV-KS has been considered an AIDS-defining condition due to presentation in the setting of severe immunodeficiency demonstrated by associated low CD4 T -cell counts and high viral loads. The introduction of antiretroviral therapy has led to a decrease in the overall incidence and prevalence of HIV/AIDS-related KS secondary to recovery of host immune response and reduction of HIV and HHV-8 viral loads. Although HAART is mainly preventative and therapeutic for clinical HIV-KS, a subset of HIV-seropositive individuals will have onset of new, worsening, or recurrent KS lesions secondary to a paradoxical phenomenon known as immune reconstitution inflammatory syndrome (IRIS) following initiation of antiretroviral therapy.

IRIS is defined as the paradoxical worsening or onset of an infection, inflammatory condition, or a proliferative disease (such as cancer) occurring in parallel with an improved immune status.[1] IRIS-induced KS is not exclusively seen in the setting of HIV-seropositivity; it has also been described in association with iatrogenic KS upon discontinuation of immunosuppressive therapy with systemic steroids and cytotoxic chemotherapy.[3]

The pathogenesis of HAART-induced IRIS-KS has been described as a dysregulation of the restored host ability to mount an inflammatory response, particularly involving the activity of HHV8 antigen.[3,6,10] A HAART-induced increase in CD4+ T cells and a decrease in HIV viral load are believed to promote the host production of inflammatory cytokines that trigger the expression of HHV-8 gene products into antigens.[3,10] The production of HHV8 antigens influences a shift from Th2 (CD4+ T-cell dominant) to Th1 (CD8+ T-cell dominant) immune response. Subsequently, this encourages production of additional inflammatory cytokines as well as cytotoxic CD8+ T cells that specifically target HHV8 antigen.[3,10] Overall, this dysregulation between the strengthened Th2 and Th1 arms of the immune system results in aberrant signaling for excessive inflammation, promotion of angiogenesis, and transformation of endothelial cells by the HHV8 antigen, all of which contribute to the angioproliferative manifestations of KS disease.

In the setting of HIV, risk factors that promote development of KS include sex between men, low CD4 T-cell count, high HIV and HHV8 viral loads, concurrent infections and history of sexually transmitted disease.[4] It has been postulated that about 6.6% to 10% of subjects who are HIV-seropositive will develop IRIS-associated KS after HAART is initiated.[6] Patients with greater immunodeficiency at initiation of HAART are at increased risk of developing IRIS, with an incidence reported as high as 25% in patients with a baseline CD4 T-cell count of <50 cells//mm^3.[6]

Diagnostic criteria for IRIS-induced HIV-KS includes a patient on HAART with new, worsening, or recurrent KS lesions in the setting of increased CD4 count greater than or equal to 50 cell/mL or a two-fold increase, and a decrease in HIV-1 viral load greater than 0.5 log.[3,6] The time frame for development of KS following initiation of HAART is not clearly defined, although several cases report cutaneous lesions developing within eight to 12 weeks of initiating therapy.[3,11]

While increased risk of IRIS is seen in the setting of advanced immunodeficiency, in recent years numerous case reports and retrospective studies have described initial KS lesions developing after initiation of antiretroviral therapy in patients with baseline CD4 counts >300 cells/mm^3 and undetectable viral loads, much like our case report.[2,5,6,12,13] The rising presentation of HIV-KS in the setting of optimally controlled HIV disease counters the traditional view that KS-lesions are a prognostic indicator specific to advanced HIV disease or that KS is an AIDS-defining illness.[2,5]

Prognosis in patients with IRIS-associated HIV-KS is promising, particularly in the setting of immunocompetence, with immunocompetence defined as undetectable viral loads and CD4 T-cell counts greater than or equal to 300 cells/mm^3. These patients have been reported to have a less aggressive course and more localized disease when compared to those who have high viral loads and low CD4 T-cell counts, or those who were HAART naïve at HIV-KS diagnosis.[4-6] These patients were also found to be significantly less likely to die and demonstrated a better 15-year survival when compared to KS patients with lower CD4 counts and detectable HIV viral loads.[5]

Optimal control of HIV infection by continuing HAART is an integral part of successful therapy, with recommended additional adjunctive local or systemic therapy depending on extent of disease.[5,7] Response to HAART as monotherapy ranges from 20% to 80% based on stage of disease and level of pretreatment.[7] Adjuvant localized therapeutic options include radiotherapy, pulse-dye laser, pulsed CO2 laser, excisional surgery, and intralesional chemotherapy. These adjuncts provide limited benefit as they do not affect development of new lesions in untreated areas, making continued therapy with HAART the only treatment associated with long-lasting, complete resolution of lesions.[5]

Conclusion

IRIS-associated HIV-KS is a paradoxical immunoinflammatory reaction brought about by improvement in immune status following antiretroviral therapy. In our current era of HAART-controlled HIV disease, dermatologists must remain suspicious of IRIS-associated HIV-KS, regardless of initial CD4+ T-cell count or HIV viral load. Judicious and appropriate screening is recommended for pre-existing KS lesions as well as for evidence of new eruptions following recovery of the immune system. This condition is best managed with continued disease control on HAART as well as adjunctive local or systemic therapy depending on clinical severity on a case-by-case basis.

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Correspondence: Marisa Wolff, DO; 518-421-4794; mhwolff@gmail.com.

Pseudoxanthoma Elasticum in Flexural and Non-Flexural Folds: A Case Presentation and Discussion

Shahrzad Akbary, BS,* Joseph Machuzak, DO, FAOCD,** Richard Bernert, MD, FASDP***

*Medical Student, 4th year, Midwestern University - Arizona College of Osteopathic Medicine, Glendale, AZ
**Board Certified Dermatologist, MacKenzie Dermatology, Prescott, AZ
***Board Certified Dermatopathologist, Arizona Dermatopathology, Scottsdale, AZ

Abstract

Pseudoxanthoma elasticum is a rare, inherited connective-tissue disorder. Characteristic cutaneous and biopsy findings typically lend to diagnosis by dermatologists. The presentation can be subtle or striking, and the disorder can involve multiple organ systems. Here we highlight an atypical cutaneous presentation of pseudoxanthoma elasticum and provide a discussion on the pathogenesis and characteristics of the disorder.

Introduction

Pseudoxanthoma elasticum, also known as Grönblad-Strandberg syndrome, is an autosomal-recessive connective-tissue disorder that results in abnormal mineralization of elastic fibers. The disease often manifests in the skin, the cardiovascular system, and the eyes. Skin findings typically occur in flexural folds and have a characteristic xanthomatous appearance; herein, we present a case of pseudoxanthoma elasticum with extensive skin involvement not limited to flexural folds.

Figure 1. Thorax, abdomen, arms; remarkable for many redundant folds.

Case Presentation

A 61-year-old male presented to our clinic for a routine skin check. Upon removal of his shirt, the patient's skin was remarkable for many redundant folds; the patient denied any history of extreme weight loss. The patient's redundant skin was diffusely distributed to his neck, underarms, thorax, abdomen, and mid to lower back. Very little of his upper body was spared aside from his upper back and face (Figures 1, 2). Upon closer examination, the skin revealed small yellow papules characteristic of a "plucked chicken skin" appearance (Figures 3, 4). The patient stated he began noticing increased sagging of his skin in his third decade of life and was subsequently diagnosed with pseudoxanthoma elasticum (PXE). Due to the extensive sagging and unique distribution of cutaneous changes, we obtained a 4 mm punch biopsy of the left abdomen to confirm his diagnosis. Biopsy revealed clumped

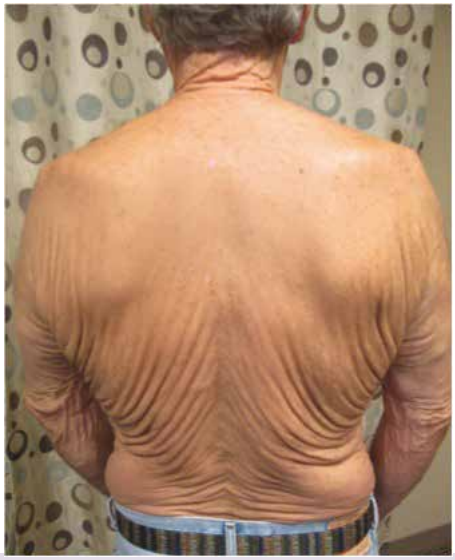

Figure 2. Redundant folds; note sparing of the upper back.

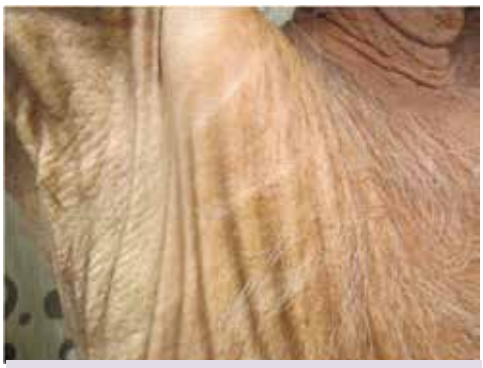

Figure 3. "Plucked chicken skin" appearance in the right axilla and chest.

and distorted elastic fibers in the reticular dermis consistent with PXE (Figure 5).

At this point, a detailed history was obtained with particular emphasis on family history and the multisystem manifestations of PXE. The patient denied any family members with known PXE or similar cutaneous manifestations; therefore, an autosomal-recessive pattern of inheritance was deemed likely. The patient also denied a history of early-onset hypertension, peripheral vascular disease, myocardial infarction, gastrointestinal bleeding, or loss of vision. He had a one-year history of hypertension and hyperlipidemia being treated with losartan and pravastatin, respectively. The patient was married and manufactured ophthalmological equipment. He had a history of tobacco use but quit in 1978. He drank two to four beers per day. He exercised 3-4 times per week at a gym for two hours at a time. When asked whether PXE had negatively affected his health, the patient stated, "If anything, I have gone out of my way to stay in shape because I have PXE." The patient continues to be seen for routine dermatologic care and has been informed of the need to monitor for extracutaneous manifestations of PXE as no specific disease-modifying treatments are available.

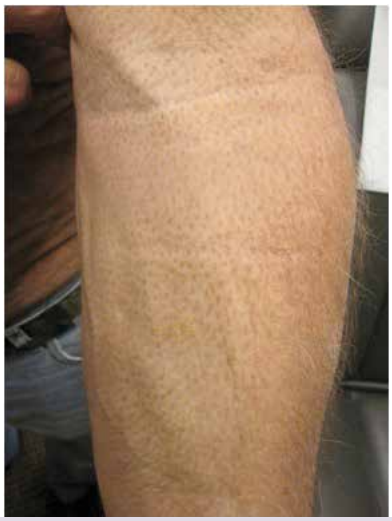

Figure 4. "Plucked chicken skin" involving and extending beyond the antecubital fossa.

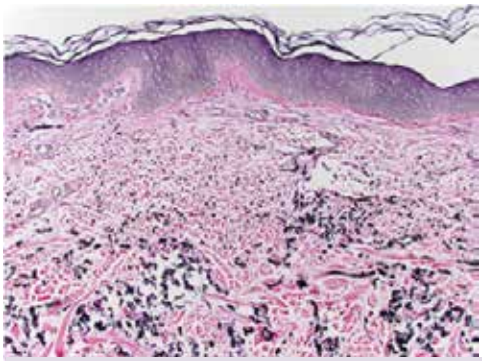

Figure 5. Elastic stain highlighting clumped and distorted elastic fibers in the deep reticular dermis; note the spared papillary dermis.

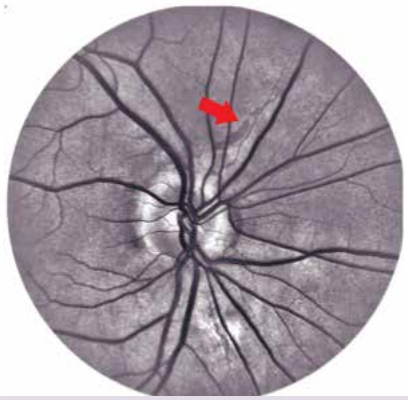

Figure 6. Right retina; arrow highlights angioid streak.

Discussion

Pseudoxanthoma elasticum is an inherited disorder that results in abnormal calcification of elastic fibers in connective tissue. The manifestations of the disease vary with the extent of connective-tissue involvement. The skin, cardiovascular system, and eyes are most commonly affected by the increased mineralization and deterioration of elastic fibers.

The prevalence of PXE is estimated to range between 1:25,000 to 1:100,000 with a slight female predominance.[1] Both autosomal-dominant and autosomal-recessive modes of inheritance have been described; however, recent studies have refuted autosomal-dominant transmission and deemed the disease as strictly autosomal-recessive.[2,3] The pathogenesis is rooted in a mutation of the adenosine triphosphate-binding cassette subfamily C member 6 (ABCC6) transporter gene on the short arm of chromosome 16p13.1. The ABCC6 transporter is found predominantly on the basolateral surface of hepatocytes and is hypothesized to serve as an efflux pump for the anti-mineralization proteins fetuin-A and matrix Gla. Therefore, loss of function of this pump results in an imbalance between anti-mineralization protection and mineral deposition. The result is increased calcification and fragmentation of elastic fibers in the aforementioned organ systems.[4]

The integumentary manifestations of PXE typically present in the patient's second or third decade of life, which accounts for a delay in diagnosis. The skin findings are classically described as being symmetric and limited to flexural folds and intertriginous areas. However, as in our case, extensive involvement beyond the typical distribution of PXE can occur. Visible to the naked eye are white-yellow papules that appear xanthomatous, hence the term "pseudoxanthoma," which coalesce to give the appearance of "plucked chicken skin." Over time, the skin becomes more lax due to lack of elastic recoil, and redundant skin folds can be seen. The dermatologic findings of PXE support a differential diagnosis that includes actinic elastosis, cutis laxa, and Ehlers-Danlos syndrome. Histologically, distorted and fragmented elastic fibers are seen in the mid to deep reticular dermis with sparing of the papillary dermis, a finding characteristic of PXE.

The vascular manifestations of PXE vary greatly and can alter the prognosis of affected patients. Abnormal calcification in the media of medium-sized vessels can predispose to accelerated coronary artery disease as well as peripheral arterial disease. Patients with known PXE should have regular visits with their primary care physician and be counseled on minimizing modifiable risk factors such as smoking.

Although they are not pathognomonic for the disease, angioid streaks are the most common ocular manifestation of PXE. Our patient was able to provide us with images of his retina from 2004 displaying this classic finding (Figure 6). The streaks are a result of breaks in the elastic-fiber layer of Bruch's membrane, the innermost layer of the choroid. While angioid streaks are often benign, neovascularization and subsequent hemorrhage can result in worsening vision and possible blindness. Therefore, patients with PXE should receive routine ophthalmologic care as well.

Conclusion

To date, there is no cure for pseudoxanthoma elasticum. Management of the condition lies in frequent monitoring for the extracutaneous manifestations of the disease as they can worsen the prognosis. While the cutaneous manifestations may seem striking to the patient, the functional capacity and integrity of the skin are not compromised. Patients should continue to see a dermatologist for annual skin checks; however, advanced precautions to protect the skin need not be taken. Treatment is deemed cosmetic and entails surgical removal of redundant skin folds by a plastic surgeon.

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Correspondence: Shahrzad Akbary, BS; 6400 E Thomas Rd. #3046, Scottsdale, AZ 85251; (818) 648-4741; sakbary81@midwestern.edu

Review of Reported Cases of Chromhidrosis

Hyunhee Park, DO,* Brad Glick, DO, FAOCD**

*Dermatology Resident, 1st year, Wellington Regional Medical Center-Dermatology Residency Program/LECOMT, Wellington, FL
**Program Director, Wellington Regional Medical Center-Dermatology Residency Program/LECOMT, Wellington, FL

Abstract

Chromhidrosis is an uncommon, idiopathic sweat-gland disorder that produces pigmented sweat. Etiology of this disorder is unknown, and the clinical presentation can vary in color of the sweat and body location involved. Histologically, chromhidrosis is notable for apocrine glands in the dermis and the presence of lipofuscin granules. There is still a controversy over the origin of chromhidrosis, whether apocrine or eccrine. There are also limited options to providing satisfactory treatment for patients suffering from this rare condition. In this review, some of the noteworthy previously documented case reports of chromhidrosis are described to illustrate the patient demographic, characteristics of the disorder in each patient reported, and treatment options explored.

Introduction

Chromhidrosis is a rare, idiopathic disorder of sweat glands, characterized by pigmented secretions from the malar cheeks, axilla, areolae, hands or other body areas. The incidence of chromhidrosis is not well-documented. Male-to-female prevalence ratio is unknown because there are too few reported cases to draw a statistically meaningful conclusion. Both the apocrine and eccrine glands can be involved in chromhidrosis. Previously reported colors of sweat include black, blue, yellow, green, red, and brown.[1-6] Although there are no known long-term sequelae associated with chromhidrosis, the condition can cause significant social and psychological distress. Treatment options for this entity are limited and still present a challenge. This article evaluates some of the previously reported cases of chromhidrosis, illustrating the demographic of the patient, body areas involved, color of the pigmented sweat, and whether the attempted treatment was successful (and if so, for what duration).

Review of the literature by case report

A 28-year-old female with a five-year history of bluish discoloration on bilateral superior cheeks was presented by Alanen et al.[5] Manual expression resulted in black sweat. Her past medical history was unremarkable, and she denied taking any medications. A 3 mm punch biopsy revealed collections of ectopic apocrine glands within mid-reticular dermis as well as occasional apocrine glands with brown lipofuscin-laden cytoplasm. This case showed an apocrine chromhidrosis involving bilateral malar cheeks in which botulinum toxin type A injection was unsuccessful. It did not disclose the methodology of botulinum toxin type A used.

On the other hand, Matarasso presented a 32-year-old female with black chromhidrosis limited to her lateral cheeks that was successfully treated with botulinum toxin type A injection.[7] This was another healthy subject with no other associated symptoms. Upon a challenge of moderate exercise (running in place), an area approximately 3.0 cm in diameter appeared with discrete pinpoint black beads just above the zygomatic arch bilaterally. Patient deferred biopsy, and trial treatment with botulinum toxin type A injection was initiated. Using a 1.0 cc tuberculin syringe, 15 units were injected into each side of the face (total of 30 units). Five injection sites were distributed at 1.0 cm intervals on each side. The patient reported there was a marked reduction in black sweat upon exertion at 48 hours. She reported a further reduction at seven days with no side effects or complications. At 14 days, the patient returned for follow-up examination, where a trace of isolated black beads of sweat reappeared in the same fashion but without pigmented sweat production. Matarasso reported these sustained results at four months post injection and indicated a substantial role of the eccrine gland in chromhidrosis.

Type A botulinum toxin is the most potent of seven subtypes: A, B, C (C alfa and C beta), D, E, F, and G. It is used as a chemodenervating agent that temporarily causes paralysis of select facial muscles, relaxing the superimposed rhytid.[7] The inhibition of acetylcholine, the neurotransmitter responsible for contracting the myoepithelium that surrounds eccrine glands, may account for the prevention of sweat release.[8] This rationale asserts that the successful response to botulinum toxin type A treatment is indicative of eccrine origin. On the contrary, there is some reported evidence that apocrine sweat glands respond to cholinergic stimulation to a lesser degree.[9] This implies that a successful response to botulinum toxin does not necessarily mean chromhidrosis is completely of eccrine origin.

Wu et al. described a 24-year-old female with black chromhidrosis involving her cheeks.[10] The patient's condition was aggravated by an increase in ambient temperature or stress level, and a black watery discharge could be expressed from her cheeks with pressure. Discharge appeared to arise primarily from the follicles along malar eminence, consistent with apocrine chromhidrosis. Biopsy was deferred, and basic laboratory workup including complete blood count, platelet count, clotting profile, urinalysis, and homogentisic levels were within normal levels. After failing a three-month course of 20% aluminum chloride hexahydrate treatment, botulinum toxin type A trial therapy was started on the patient's right cheek. Ten units were injected intradermally to the visible chromhidrosis area in five-unit amounts approximately 1 cm apart. Less-prominent discoloration was noted at three-week follow-up with no side effects, and 10 more units of botulinum toxin type A were injected into the areas of the right cheek in a similar fashion. The patient reported significant reduction in sweating as well as substantial decrease in discoloration at two weeks post-injection. There was still beneficial response present at 19 weeks post-treatment. The article did not mention why the right cheek was chosen for the trial treatment or why bilateral treatment was not done.

Chromhidrosis has been reported in male patients. A 38-year-old man with a five-year history of dark blue secretions on bilateral malar cheeks was reported in an article by Chang et al.[11] Pinpoint pigmented specks were limited to his cheeks and would appear with exertion in a symmetric, diffuse pattern. His medical history was unremarkable, with no topical or oral medications. Urinary homogentisic acid levels and lumbar spinal X-rays were normal. A 3 mm punch biopsy revealed glandular structures exhibiting decapitation secretion, consistent with ectopic apocrine glands in the deep reticular dermis.[11] Also, bluish cytoplasmic granules were observed in the apocrine epithelium lining, leading to a diagnosis of facial apocrine chromhidrosis. The patient denied any active treatment at that time.

Malar cheeks are a frequently reported body site for chromhidrosis; however, other locations have been addressed in the literature. Polat et al. described a case of a 44-year-old woman with

a 10-month history of blue staining of clothing around the breasts and axillae.[12] Her medical history was insignificant, and she was not taking any medications. Physical examination revealed blue staining on the patient's bra with no other abnormal findings. Mycological and bacteriological cultures from the axillae and inframammary region grew no organisms.[12] The patient refused a biopsy, and this report does not mention whether treatment was attempted.

Although chromhidrosis seems most commonly limited to one area of the body, it is possible to involve more than one body area as reported by Perez Tato et al. in 2012.[13] They reported a case of 26-year-old woman with a three-year history of dark blue secretions on bilateral malar cheeks. On examination, a subtle blue sweating of her axillae was noted. In this case, a 4 mm punch biopsy was obtained from the axillary region, showing apocrine glands in the deep reticular dermis as well as bluish lipofuscin granules in the apocrine epithelium lining. This confirmed the diagnosis of apocrine chromhidrosis, and treatment with 20% aluminum chloride hexahydrate solution was initiated with poor tolerance due to irritation. Topical capsaicin cream was tried later, again with poor tolerance secondary to burning sensation. Subsequently, treatment with botulinum toxin type A was started with 10 units into each side of the face, 0.05 cc per injection site. Authors reported a reduction in sweating and a decrease in discoloration at one week after injection. Although without complete remission, improvement persisted at four months post treatment.

Conclusion

Chromhidrosis is a rare, idiopathic sweat-gland disorder characterized by the excretion of pigmented sweat arising from either apocrine or eccrine glands. Clinically, it is sometimes difficult to distinguish between eccrine and apocrine origin. As mentioned previously, there remains some controversy as to whether the resolution of chromhidrosis with botulinum toxin injections is indicative of a purely eccrine nature, because there is some evidence reported that apocrine glands are also affected. In apocrine chromhidrosis, varying degrees of oxidized lipofuscin pigment granules within apocrine glands can cause black, blue, green, brown, red, and yellow sweat.[14] The presence of lipofuscin pigment granules within the apocrine cells confirms the diagnosis of apocrine chromhidrosis.[2] Eccrine chromhidrosis is the excretion of pigmented sweat from eccrine glands after the ingestion of dyes or drugs, and red, yellow, and blue excretions have been described in the literature.[14] Pseudochromhidrosis is the change of color of normal sweat on the skin by surface compounds, molecules, or chromogenic bacteria. Such chromogens include dyes, colored chemicals, or microorganisms such as Piedraia or Corynebacterium.[7,15,16]

Three main off-label treatment options for chromhidrosis include topical capsaicin cream, 20% aluminum chloride hexahydrate solution, and botulinum toxin A. Satisfactory therapy for chromhidrosis remains challenging and is typically focused on ways to reduce secretions. It is worthwhile to explore new technologies such as micro-focused ultrasound to reduce sweat production as potential chromhidrosis treatment options.[17]

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Correspondence: Hyunhee Park, DO; hparkdo@gmail.com

Acquired Bilateral Nevus of Ota–like Macules (Hori's Nevus): A Case Report and Treatment Update

Jamie Hale, DO,* David Dorton, DO,** Kaisa van der Kooi, MD***

*Dermatology Resident, 2nd year, Largo Medical Center/NSUCOM, Largo, FL
**Dermatologist, Teaching Faculty, Largo Medical Center/NSUCOM, Largo, FL
***Dermatopathologist, Teaching Faculty, Largo Medical Center/NSUCOM, Largo, FL

Abstract

This is a case of a 71-year-old African American female who presented with bilateral periorbital hyperpigmentation. After failing treatment with a topical retinoid and hydroquinone, a biopsy was performed and was consistent with acquired bilateral nevus of Ota-like macules, or Hori's nevus. A review of histopathology, etiology, and treatment is discussed below.

Introduction

Acquired nevus of Ota-like macules (ABNOM), or Hori's nevus, clinically presents as bilateral, blue-gray to gray-brown macules of the zygomatic area. It less often presents on the forehead, upper outer eyelids, and nose.[1] It is most common in women of Asian descent and has been reported in ages 20 to 70. Classically, the eye and oral mucosa are uninvolved. This condition is commonly misdiagnosed as melasma.[1] The etiology of this condition is not fully understood, and therefore no standardized treatment has been established.

Case Report

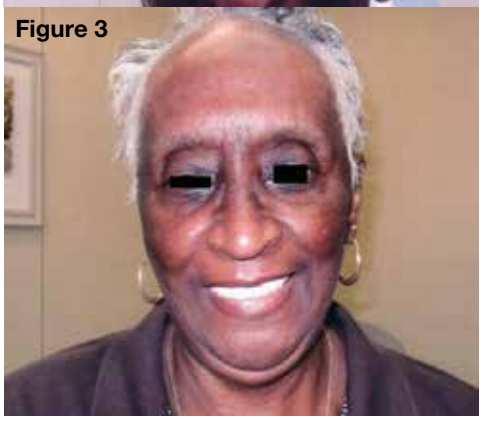
A 71-year-old African American female initially presented with a two week history of a pruritic, flaky rash with discoloration of her face. She stated she had a mask placed on her face during a facial one week prior, but the discoloration was present prior to the facial treatment. She denied any use of new products and stated her only new medication was ciclesonide nasal aerosol, prescribed by her allergist. Her past medical history was only significant for hypertension. The patient denied a family history of similar lesions or facial discoloration. Her current medications included amlodipine, aspirin, flax seed oil, glucosamine, hydrochlorothiazide, omega 3 fish oil, and vitamin B12.

On physical exam, she was noted to have very well demarcated hyperpigmentation affecting the majority of her forehead and periorbital region with Fitzpatrick type IV skin (Figures 1-3). The patient was sent for labs including TIBC, iron, ACTH, and free and total testosterone, and all were within normal limits. She was given a recommendation to see her allergist regarding the possibility of her new medication causing the hyperpigmentation. She was also advised to try skin-lightening products, including kojic acid and hydroquinone 2% cream, as well as to wear sunscreen and protective clothing to avoid UV exposure. The patient was also notified that amlodipine can cause skin pigment changes, and HCTZ can cause photosensitivity, but was told not to discontinue any medications without speaking with her primary care physician.

Figure 1

Figure 2

Figure 3



Six months later, the patient presented for re-evaluation. Her hyperpigmentation remained unchanged with topical hydroquinone 2% cream and tretinoin 0.05% gel. At this visit, a punch biopsy of her left zygoma was performed. Histopathology reported sparse proliferation of irregularly shaped, haphazardly arranged melanocytes extending from the superficial reticular dermis to mid-deep reticular dermis (Figures 4, 5). A Mart-1 (Figure 6) and S100 stain were used to confirm the presence of dermal spindled melanocytes. Due to its acquired bilateral presentation, it was most consistent with Hori's nevus.

Figure 4

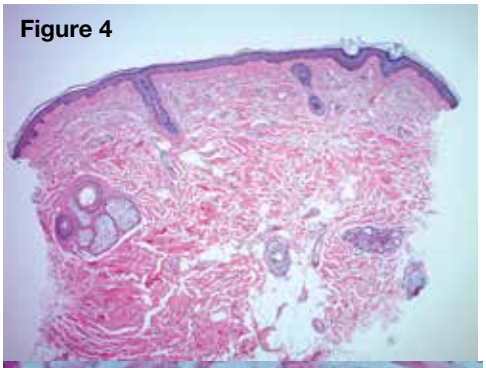


Figure 5

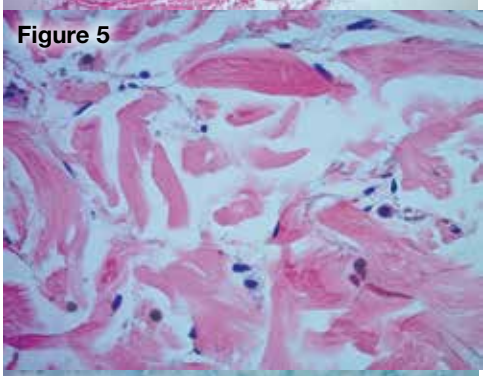
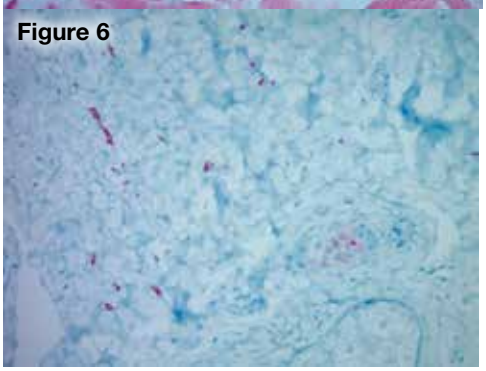


Figure 6



Discussion

ABNOM was first described by Hori et al. in 1984, and its alternate designations include nevus fusco-caeruleus zygomaticus and acquired circumscribed dermal facial melanocytosis.[2] Histologically, it is characterized by irregularly shaped, bipolar melanocytes in the papillary and mid dermis without disruption of the normal skin architecture. On electron microscopy, the melanosomes of ABNOM are mainly singly dispersed and in stages II, III, and IV. ABNOM differs clinically from nevus of Ota, as it often presents in late adulthood, is bilateral, may be speckled or confluent, and does not involve the mucosa.[3] In addition to nevus of Ota, the differential diagnosis of ABNOM includes melasma, lentigines, and dark circles under the eye.[4]

Despite the relatively common occurrence, the pathogenesis of ABNOM is not well understood. There are currently several mechanisms that have been described to account for the origin of the melanocytes. The first, described by Hori et al., states that the melanocytes descend from the epidermis to the dermis to create the darker bluish-gray hue.[2] Dermal inflammation or atrophy could potentially be reactivating preexisting melanocytes, which would explain the presence of dermal melanocytes in uninvolved skin near the pigmented macules.[5] Another potential etiology is the migration of hair bulb melanocytes.[6] Pistone et al. used confocal microscopy to describe melanocytes of the hair follicle proliferating and appearing to migrate up the outer root sheath, later repopulating interfollicular epidermis. Their study further stated that these melanocyte stem cells appear to have the capability to enter vacant niches, including migration to the epidermis.[7]

Multiple factors have been considered to induce ABNOM, including UV light, the most probable cause, as well as sex hormone changes. Murakami et al. reported cases of ABNOM induced by atopic dermatitis, which further points to chronic inflammation playing a causal role as well as the possibility of histamine and stem cell factor (SCF) involvement.[8] This hypothesis was supported by Lee et al., whose study described increased expression of the SCF/c-kit pathway between dermal fibroblasts and dermal melanocytes. This study also highlighted the lack of epidermal pigmentation involved in the condition, supporting the idea that topical bleaching treatment may be unnecessary prior to laser therapy.[9] A study by Long et al. demonstrated that a significant percentage of ABNOM expressed androgen receptor; however, estrogen-receptor and progesterone-receptor expression was not identified despite previous theories stating their involvement in the pathogenesis. This will require further studies to confirm, but it raises the possibility of topical use of selective androgen-receptor modulators as targeted therapy for some patients.[10] There has been no direct genetic locus described, but case series with family history and genetic associations have been documented.[11]

Treatment of ABNOM can be difficult, and many modalities have been described including cryotherapy, dermabrasion, chemical peeling, topical agents, and laser therapy. Topical treatments used to treat ABNOMs with varying success include hydroquinone, tretinoin, corticosteroids, glycolic acid, and azelaic acid.[12] The disappointing results of topical therapies are likely due to the deep-seated nature of the melanocytes in this condition. Therefore, laser therapy is often required for treatment. Noted in the literature is the use of Q-switched ruby, Q-switched alexandrite, and Q-switched Nd:Yag lasers.[13] Location of these lesions, as well as the prevalence in higher Fitzpatrick skin types, poses therapeutic dilemmas. Often, multiple laser treatments are needed to achieve desired results.[13] Manuskiatti et al. described the efficacious use of Q-switched ruby laser following a scanned CO2 laser with no long-term adverse sequelae and decreased number of treatments required.[14] Post-inflammatory hyperpigmentation is often problematic in this patient population and can be reduced by applying corticosteroids immediately post laser.[12] Therapeutic response is also largely dependent on the baseline and predominant color of the nevus.[14]

Conclusion

To-date, our patient has elected to treat only with topical tretinoin and hydroquinone. She was advised that laser therapy would be the best option should she desire more aggressive treatment. Hori's nevus, or ABNOM, is a relatively common entity with an etiology that is not well understood but includes possible inflammatory, hormonal, and ultraviolet stimulation. It is commonly misdiagnosed as other entities including melasma or solar lentigines. A multi-modality, patient-specific and lesion-specific treatment approach is necessary to achieve optimal results. Finally, when treating with laser therapy, multiple treatment sessions and multiple lasers may be necessary.

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Correspondence: Jamie Hale, DO; Largo Medical Center, 201 14th St SW, Largo, FL 33770; Ph: 727-588-5200; F: 727-608-4531; jamiedhale@gmail.com

Dowling-Degos Disease: A Case Report

Megan Joint, DO,* Michael Garone, DO,** Erica Rushing, MD,***Natalie Depcik-Smith, MD,**** Daniel Hurd, DO, FAOCD*****

*Dermatology Resident, 1st year, LewisGale Hospital Montgomery/VCOM, Blacksburg, VA
**Medical Student, 4th year, West Virginia School of Osteopathic Medicine, Lewisburg, WV
***Dermatopathologist, Greensboro Pathology Associates, Greensboro, NC
****Dermatopathologist, Greensboro Pathology Associates, Greensboro, NC
*****Program Director, LewisGale Hospital Montgomery/VCOM, Blacksburg, VA

Abstract

Dowling-Degos disease is an uncommon genodermatosis characterized by acquired, reticulated flexural hyperpigmentation. We present the case of a patient with pruritic hyperpigmentation of the chest and asymptomatic flexural hyperpigmentation. A literature search revealed multiple case reports, which have been reviewed and presented here. The differential diagnosis includes acanthosis nigricans, neurofibromatosis type 1, and multiple variants of Dowling-Degos such as Galli-Galli disease, Haber syndrome, dyschromatosis symmetrica hereditaria, and reticulate acropigmentation of Kitamura.

Introduction

Dowling-Degos disease is an uncommon genodermatosis for which there is limited up-to-date information in the literature. The small number of case reports makes the disease difficult to recognize, so it can be a challenging diagnosis to make. Classically, DDD is a benign disorder of hyperpigmentation that develops in early adulthood and may be asymptomatic or pruritic. However, there are less-common presentations, including a case described in 2012 by Pickup and Mutasim of a patient with asymptomatic hypopigmented lesions.[33] We present the case of an adult patient with more characteristic exam findings who wasn't even aware she had a skin condition. Although patients may not be concerned, this diagnosis is important to make as the condition imparts an increased risk of certain types of cutaneous squamous cell carcinoma.

Case Report

A 59-year-old Caucasian female presented with a 12-month history of pruritic, scaly patches on the sun-exposed chest and extremities that had been treated with intralesional steroids without improvement. When asked about an incidental exam finding of flexural freckling, the patient stated she'd had it her entire life. She denied exacerbating or alleviating factors. It had never been treated. Past medical history and medications were noncontributory. Family history was positive for similar freckling in two sisters as well as the patient's mother.

Figure 1. Left axilla

Physical exam revealed multiple erythematous, scaly papules and plaques on the central chest and bilateral shins, consistent with disseminated actinic porokeratosis. In addition, symmetric, reticulated dark brown macules were noted on the neck, axillae, inframammary and inguinal folds, popliteal fossae, and chest (Figures 1, 2). Pitting scars were present on both of the oral labial commissures.

Histologic sections of a punch biopsy from the left axilla revealed a normal, basket-weave stratum corneum overlying a slightly thinned epidermis. Finger-like projections of hyperpigmented rete ridges were seen, with more pronounced pigmentation at the tips of the rete. Occasional horn cysts were present. The infundibular portion of the hair follicle was dilated. The thin, branching, pigmented projections involved the infundibula of the follicles, which is characteristic of Dowling-Degos disease. There was also a mild, superficial, dermal perivascular lymphocytic infiltrate with occasional pigment-laden macrophages (Figures 3, 4). A diagnosis of Dowling-Degos disease was made.

Figure 2. Left popliteal fossa

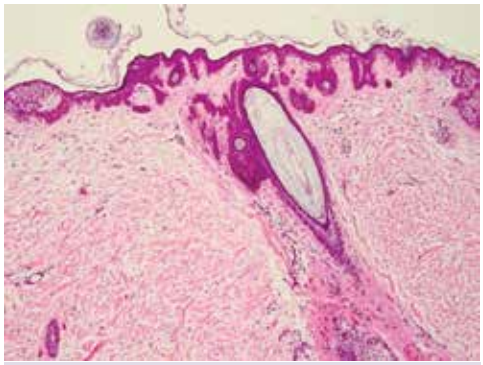

Figure 3. Punch biopsy of left axilla demonstrating involvement of the follicular infundibulum.

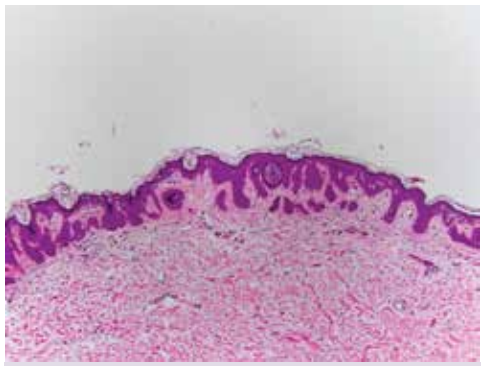

Figure 4. Finger-like projections of hyperpigmented rete ridges and horn cysts.

Treatment included a mixture of CeraVe™ cream and clobetasol solution used twice daily until her three week follow-up, at which time the frequency of use was decreased. Claritin 10 mg three times daily was also recommended, and the patient reported alleviation of her symptoms.

Discussion

Dowling-Degos disease (DDD) is an uncommon genodermatosis characterized by a reticular

pigment pattern that is most pronounced in flexural areas. It was first described in 1938 by Dowling and Freudenthal.[1] In 1954, Degos and Ossipowski termed the disease "dermatose réticulée des plis."[2] DDD can be inherited as an autosomal-dominant mutation, or it can occur sporadically.[3,4] There is no racial predisposition; however, there may be a predilection for females.[5,6] The disease results from a loss-of-function mutation in the keratin 5 gene (KRT5).[5,7] One case report of a family with DDD demonstrated a frameshift mutation in the V1 domain of KRT5.[8] This gene is partly responsible for melanosome trafficking from melanocytes to keratinocytes. There are different variations of DDD, and it is likely that these variations are a result of different mutations within KRT5.

Signs and symptoms manifest around the third to fourth decades of life; however, it has been described in newborns.[9] Brown-to-black macules and papules with variable hyperkeratosis arranged in a reticulated pattern are most prevalent at intertriginous sites.[10,11] Commonly involved areas are the axillae, groin, inframammary folds and neck. The disease progresses over time and can involve less-common locations such as the intergluteal folds, trunk, inner thighs, upper arms, and face.[12,13] The pigment pattern can be localized or generalized. Speckled macules may be found on the external genitalia in males and females.[14-16] The main symptom reported is pruritus localized to the hyperpigmentation.[11] Appearance can worsen during summer months. Additional findings include hypopigmented macules and papules, comedone-like lesions, fingernail dystrophy, and pitted perioral scars.[11] There are several reports of an increased prevalence of epidermal cysts, hidradenitis suppurativa, keratoacanthomas and perianal squamous cell carcinoma among those diagnosed with DDD.[17-21]

Histologically, there is increased pigment along the basal layer with elongated rete ridges and thinning of the suprapapillary epithelium.[22,23] This has been referred to as an "antler-like" pattern. There is also a mild perivascular lymphohistiocytic infiltrate present along with dermal melanophages.[11] Galli-Galli disease, one of the variants, also features acantholysis with parakeratosis.[24,25] The histologic features of Dowling-Degos disease are similar to those seen in an adenoid seborrheic keratosis; however, clinical history and infundibular follicular involvement can help differentiate between the two entities.

The differential diagnosis of DDD includes acanthosis nigricans, which differs both clinically and histologically. Clinically, velvety plaques help to distinguish the two. Histologically, the rete ridges are not as elongated in acanthosis nigricans, and there is no follicular component. Neurofibromatosis type 1 is also in the differential, but the age of onset and clinical picture make the two easily distinguishable.

There are several variants of DDD that result in many experts considering the disease as a spectrum. Localized and generalized Dowling-Degos and Galli-Galli disease were discussed above. Haber syndrome presents with rosacea-like facial redness beginning in childhood along with keratotic papules, comedones, scars, and reticulated hyperpigmentation on the trunk, proximal extremities, and axilla.[26] Dyschromatosis symmetrica hereditaria (DSH) is another variant that appears during infancy as hyper- or hypopigmented macules on the dorsal hands.[27] Dyschromatosis universalis hereditaria is similar but has more generalized pigmentation than DSH.[28] Reticulate acropigmentation of Kitamura (RAPK) consists of pigmented freckles on the dorsum of the hands and feet, palmar pits, epidermoid cysts, hypopigmented macules and papules, and discontinuity of dematoglyphics.[29] Signs and symptoms typically start to develop around adolescence. There is some controversy as to whether or not RAPK is a distinct entity from DDD. A recent study identified a mutation in the ADAM10 gene as the cause of RAPK and proposed to classify it as a distinct disease.[30]

The diagnosis of DDD is made based on clinical features and histopathologic findings. There have been no successful treatments for DDD.[11] Topical steroids, azelaic acid, topical and systemic retinoids, and hydroquinone have been used with varying success. One case report demonstrated success in treating the pruritus and pigmentation with adapalene; however, once treatment was stopped the lesions and symptoms reappeared. Improvement of lesions with the erbium:YAG laser has been reported.[31,32]

Conclusion

Dowling-Degos disease is an uncommon entity with multiple variants that are often considered to lie on a disease spectrum. Although limited to the skin and relatively harmless, it is important to diagnose the condition as these patients can have increased risk of other, concerning cutaneous diseases.

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Correspondence: Megan Joint, DO; 2617 Sheffield Drive, Blacksburg VA 24060; Ph: 540-953-2210; Fax: 540-951-9112; meganjo@pcom.edu

An Unusual Case of Henoch-Schönlein Purpura in an Elderly Male

Jeffrey Kushner, DO,* David Posnick, DO,** Joan M. Mones, DO,*** Adriana Ros, DO, FAOCD***

*PGY-1 Traditional Rotating Intern, Largo Medical Center, Largo, FL
**PGY-3 Dermatology Resident, Palisades Medical Center, North Bergen, NJ
***Program Director, Dermatopathology Fellowship, New York College of Osteopathic Medicine/Ackerman Academy of Dermatopathology, New York, NY
****Program Director, Dermatology Residency, Palisades Medical Center, North Bergen, NJ

Abstract

Henoch-Schönlein purpura (HSP) is a subset of cutaneous small vessel vasculitis (CSVV) characterized by IgA deposition in the walls of small blood vessels leading to non-thrombocytopenic palpable purpura, typically of the lower extremities. Other immune factors such as IgM, IgG, complement, and fibrinogen may be found in vessels. The disease is characterized by a tetrad of manifestations including palpable purpura, arthralgia/arthritis, abdominal pain, and renal disease.[1] Morbidity in the HSP patient population is correlated with chronic renal failure secondary to glomerulonephritis. HSP is rarely seen in the adult and geriatric population; approximately 90% of patients are children. We present a case of HSP in a nonverbal, nonambulatory 62-year-old Caucasian male.

Introduction

Henoch-Schönlein purpura (HSP) is a cutaneous small vessel vasculitis with deposition of IgA and other immune factors within the vessel walls. The disease was originally identified in 1801 by Johann Schönlein and his student, Eduard Henoch, who described the clinical signs and symptoms.[1] It is highlighted by a tetrad of symptoms and complications—palpable purpura, arthralgia/arthritis, abdominal pain, and renal disease. Although HSP is significantly more common in the pediatric population, failure to diagnosis and treat adults can have serious ramifications. We report a case of HSP in a 62-year-old patient with an extensive past medical history who initially presented to the clinic with a lower extremity rash.

Case Report

A 62-year-old, minimally verbal, non-ambulatory Caucasian male presented to the dermatology outpatient clinic complaining of a new-onset rash on his lower extremities for one week. The patient denied any symptoms of itching or pain. Clotrimazole/betamethasone topical cream prescribed by his internist showed no improvement. The patient reported no known allergies and no significant family history of vasculitis or autoimmune disease. The patient's extensive past medical history included: congestive heart failure, cerebral vascular accident, dementia, epilepsy, and dysphagia. Medication list included clonazepam, warfarin, phenytoin, simvastatin, digoxin, furosemide, and diltiazem. The patient did admit to a history of tobacco use.

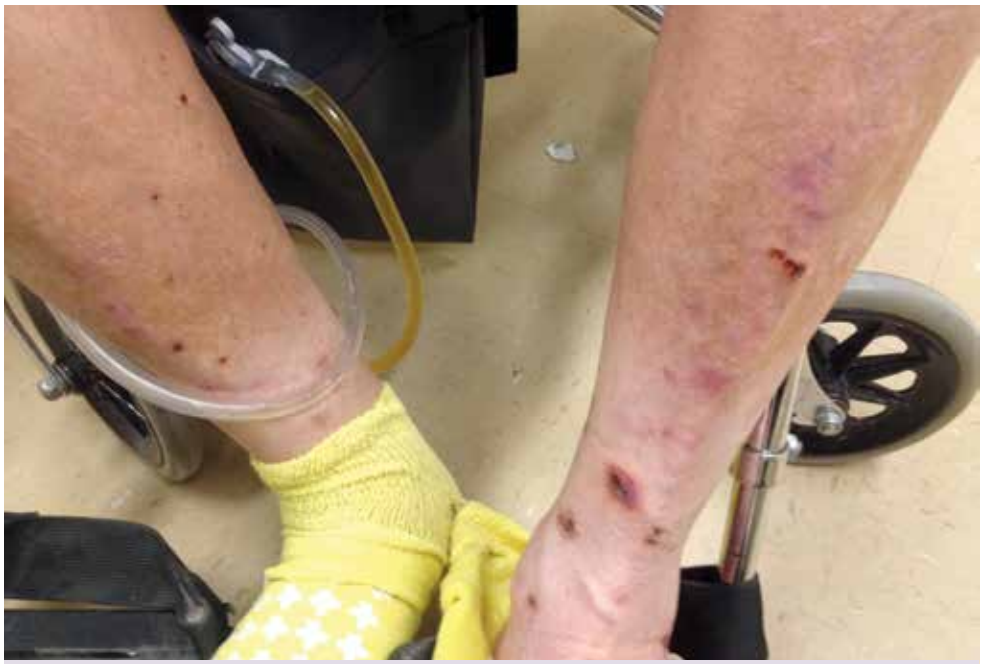

Figure 1. Multiple discrete, non-blanchable, purpuric papules with hemorrhagic crust on the anterior lower legs symmetrically.

Physical exam revealed multiple discrete, non-blanchable, purpuric papules with hemorrhagic crust on the anterior lower legs symmetrically (Figure 1). Provisional diagnoses included: leukocytoclastic vasculitis secondary to drug, connective-tissue disease or HSP, folliculitis, neurotic excoriations, scabies, insect bites, lymphomatoid papulosis, and pityriasis lichenoides et varioliformis acuta.

Two 3 mm punch biopsies were performed and sent for routine hematoxylin and eosin (H&E) staining and direct immunofluorescence (DIF). One biopsy was obtained from the left superior lateral tibia and another from the left inferior medial tibia. A complete metabolic panel, complete blood count with differential, urinalysis, and hepatitis panel were ordered. Labs on the patient were unremarkable except for anemia (hemoglobin 11.1). Renal function was stable (BUN: 11 creatinine: 0.6). H&E biopsy showed evidence of early leukocytoclastic vasculitis (Figure 2). DIF studies were compatible with

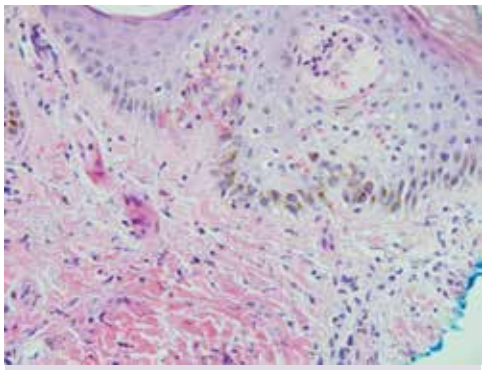

Figure 2. The changes of early leukocytoclastic vasculitis, including increased numbers of neutrophils, incipient nuclear dust of neutrophils, and extravasation of erythrocytes (H&E stain).

HSP/IgA vasculitis (Figure 3). There was also granular perivascular deposition of C3 and smooth perivascular deposition of fibrinogen but no perivascular deposition of IgM on DIF. Treatment plan included clobetasol 0.05% ointment every 12 hours to the lower extremities for two weeks as well as nephrology consultation (pending).

Discussion

HSP has an annual incidence of about 20 per 100,000 children less than 17 years of age with a peak incidence of 70 per 100,000 in children between the ages of four and six years old.[2] There is a slight male predominance. The disease occurs less frequently in African Americans, and is more prevalent in the fall and winter months. The incidence of HSP in the adult population is approximately 1.3 per 100,000 patients, and data on the elderly population is even more sparse.[3,4]

While HSP is associated with deposition of IgA in small blood vessels, there has also been literature reporting alterations in glycosylation of IgA and elevated levels of IgA anticardiolipin antibodies.[1] In adults, vascular IgA deposits are highly specific for HSP, although not all patients may have a positive DIF.[11] Additionally, complement activation, glomerular crescent formation and vascular damage have been identified as important mechanisms underlying renal involvement in HSP. Multiple triggers for the condition have been suggested, although the actual cause still remains unknown. In children, symptoms may be preceded by an upper respiratory infection, more specifically attributed to group A beta-hemolytic streptococcus.[3] Multiple disease states and drugs have been implicated in the development of HSP including pregnancy, α1-antitrypisin deficiency, alcohol, vaccinations, chlorpromazine, losartan, aspirin, and antimicrobials such as penicillin, ampicillin, clarithromycin, and erythromycin.[4-6]

HSP is characterized by both cutaneous and extracutaneous manifestations. Children almost universally present with erythematous, urticarial papules that rapidly develop into petechiae and palpable purpura. Vesicles, bullae and necrotic ulcers may also be present. The most common locations for these findings are on pressure-dependent areas such as the buttocks and lower extremities, although the elbow and knees may also be involved.[7] Individual lesions usually fade within a week, resulting in hyperpigmentation, although recurrent lesions are possible. Cumulative skin manifestations usually last for six to 16 weeks, although 5% to 10% of patients

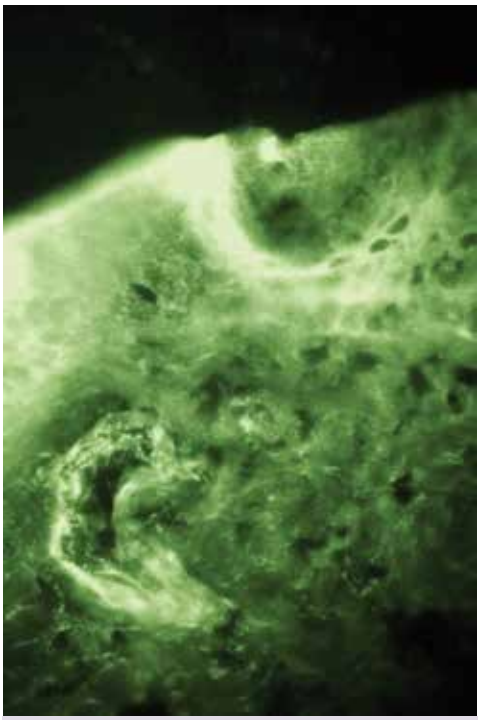

Figure 3. Granular perivascular deposition of IgA present in superficial dermal blood vessels (direct immunofluorescence).

will develop chronic cases.[1]

Commonly reported extracutaneous manifestations include arthritis, abdominal pain, and renal disease. Of the reported symptoms, joint pain was the most common extracutaneous manifestation, occurring in up to 84 percent of patients.[1] The pain is usually transient and oligoarticular and often afflicts the lower extremities, resulting in pain with ambulation. Gastrointestinal symptoms are varied, ranging from mild nausea, vomiting and abdominal pain to more emergent cases of intussusception, bowel ischemia and perforation. The abdominal pain has been attributed to submucosal hemorrhage and edema. In cases with gastrointestinal involvement, subclinical laboratory findings that may indicate more advanced disease include a positive fecal occult blood test, hypoalbuminemia and a positive α_1-antitripysin.

Adult manifestations of HSP do not necessarily present like those seen in the pediatric population. When compared to children, adults have a lower incidence of prior upper respiratory infection upon development of HSP. Abdominal pain and fever are less prevalent during the course of the disease in adults, while joint complaints and renal disease are increased.[7] A higher frequency of nephrotic syndrome, hypertension and elevated serum creatinine may be seen in the adult population, which can be especially concerning in the presence of comorbidities.[8,9] Furthermore, literature suggests that renal manifestations become even more prominent in elderly patients compared to adults less than 60 years old.[4]

A clinical diagnosis of HSP is usually made in children with the prevalence of cutaneous and extracutanous manifestations, which are often present. However, the varied presentation in adult patients may prove more challenging diagnostically. Purpura can be seen with infection, hypersensitivity vasculitis, rheumatoid arthritis, and other small vessel vasculitides. These can include granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).[1] Rheumatoid arthritis and systemic lupus erythematosus can mimic the joint complaints, while IgA nephropathy or Berger's disease could present similar renal findings.[8]

A definitive diagnosis is usually based upon both clinical manifestations and biopsy. A biopsy is more valuable in the adult population because HSP is less common and extracutaneous symptoms are not always apparent. When assessing skin histopathology, proper sampling techniques are paramount to yielding accurate diagnostic results. A punch biopsy from the edge of a fresh lesion, ideally less than 24 hours old, is the most effective and accurate technique.[5] On

H&E staining, tissue will show a leukocytoclastic vasculitis secondary to deposition of IgA within postcapillary venules in the papillary dermis.[1] Additionally, neutrophils and monocytes comprise the inflammatory infiltrate in most cases. Direct immunofluorescence (DIF) of the vessels will demonstrate perivascular IgA, C3 and fibrin deposits.[1,5]

Additional laboratory testing such as a complete blood count, serum chemistries, coagulation studies, and a urinalysis should be considered, especially when a diagnosis is questionable. Urinalysis may reveal microscopic hematuria, macroscopic hematuria, proteinuria, or cellular casts. In select patients, a renal biopsy might be warranted, possibly showing a wide range of glomerular changes on both light microscopy and immunofluorescence.[8] Abdominal radiographs and ultrasonography may be considered if the patient also has abdominal complaints.

HSP is usually self-resolving, although supportive, symptomatic and disease-modifying approaches have been proposed. Hydration, rest, and pain relief with analgesics should be considered if there are no contraindications. Hospitalized patients must be monitored for surgical abdomen, intracranial hemorrhage, anemia, hypertension and electrolyte disturbances. Parenteral nutrition must be considered in patients with severe abdominal symptoms. NSAIDs should be strongly considered for pain relief. While they do not increase the risk of GI hemorrhage, patients should be assessed for current GI bleeding before administration. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are utilized for their antihypertensive effects and also have proven effective in slowing the progression of kidney disease. Glucocorticoids have been reported to shorten the duration of abdominal symptoms, decrease risk of recurrence, and decrease renal involvement.[10] However, the long-term benefits of steroid administration are mixed, so the cost/benefit must be assessed on an individual basis.

Additionally, other multi-drug regimens that include azathioprine, cyclophosphamide, and dipyridamole have been utilized. Cyclophosphamide in particular is often used in conjunction with steroids to help alter the disease course. Case reports have also shown positive results with the use of rituximab in patients refractory to both steroid and cyclophosphamide combinations.[13] Furthermore, plasma exchange has showed promising results in patients with severe initial presentations of HSP.[14] Early research in experimental models has explored the possible role of IL-1 receptor antagonists in reducing adhesion molecules and subsequent crescent formation.[15]

Morbidity and mortality of HSP are usually correlated with severity of renal disease. Patients with biopsy findings of nephrotic syndrome, renal insufficiency, hypertension, crescentic glomerulonephritis, and tubulointerstitial fibrosis have a worse prognosis.[8] However, it was shown that the severity of pathology (graded I-V) was more predictive of outcome compared to initial clinical presentation.[12] Of note, newer literature recommends further histological classification of the pathology in an attempt to detail the disease progression and predict the response to therapy. The characteristics proposed are more than just crescent formation and include: mesangial hypercellularity, endocapillary hypercellularity, crescents, segmental and global glomerulosclerosis, arteriolosclerosis, interstitial inflammation, and tubular atrophy/interstitial fibrosis.[16] Although the literature is mixed, 10% to 30% of adults with HSP will progress to end-stage renal disease within 15 years. As a result, patients should be periodically monitored for worsening renal function and treated accordingly.

Conclusion

HSP is a well-documented clinical disease in children, but is much less common in adults, especially in the elderly. Although HSP histology is difficult to distinguish from that of LCV, vascular IgA is specific, but not sensitive, for HSP. The constellation of palpable purpura, arthralgia/arthritis, abdominal pain and renal complications usually aid in the diagnosis. However, it is important to consider HSP in patients with cutaneous findings and a lack of systemic complaints, even in the elderly population. The fact that our patient was both nonverbal and nonambulatory complicated the diagnosis by limiting our ability to clinically evaluate extracutaneous findings.

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Correspondence: David Posnick, DO; Palisades Medical Center, 7912 River Rd, North Bergen, NJ 07047; 603-689-6390; dposnick44@gmail.com

PLEVA in an Adult Patient with an Unclear HSV Association

Alyson Snyder, BS,* G. Trey Haunson, DO,** Michael Conroy, MD,*** Daniel S. Hurd, DO, FAOCD****

*OMS-III, Edward Via College of Osteopathic Medicine, Blacksburg, VA
**PGY-4 resident, LewisGale Hospital Montgomery, Blacksburg, VA
***Dermatopathologist, Dermatopathology Laboratory of Central States, Dayton, OH
****Program director, Dermatology Residency Program, LewisGale Hospital Montgomery, Blacksburg, VA

Abstract

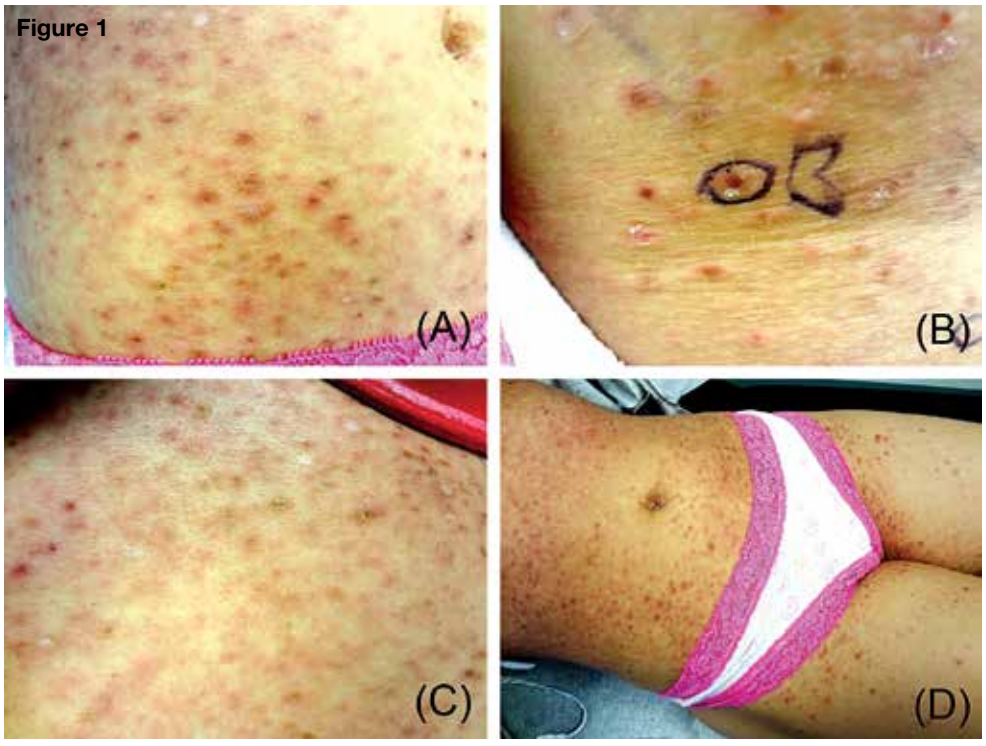
Pityriasis lichenoides et varioliformis acuta (PLEVA) is a rare clonal T-cell disorder typically affecting pediatric patients. It is characterized by an acute, self-resolving pleomorphic cutaneous eruption with an unpredictable relapsing and remitting clinical course. PLEVA has been associated with various infections and medications. We report the case of a young, otherwise healthy, adult female with PLEVA.

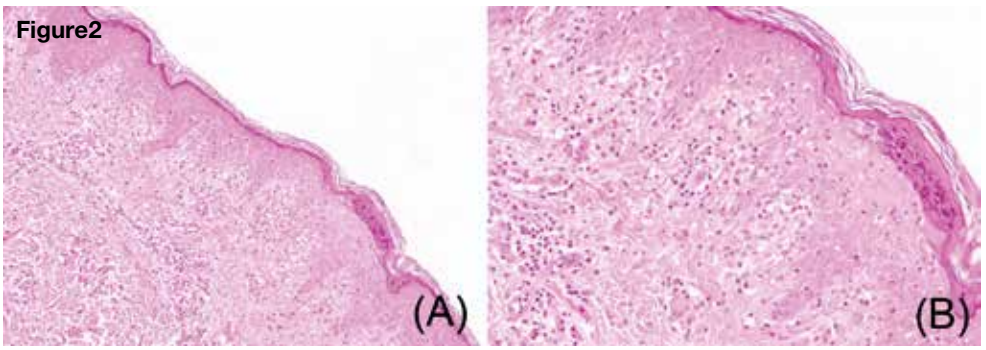
Case Report

A 22-year-old female presented with a two-week history of a worsening acute, pruritic and slightly "burning" rash all over her body. She had seen her primary care physician twice at referral, initially when the rash was confined to her upper chest, and was placed on oral clindamycin. She returned when the rash continued to spread. Bacterial cultures yielded coagulase-negative staphylococcus, and she was given oral methylprednisolone taper and oral doxycycline.

She had a past medical history of attention deficit disorder and depressive/anxiety disorder. Her current medications included an oral contraceptive pill that she restarted *after* the rash appeared, escitalopram oxalate 10 mg daily, and methylphenidate 10 mg twice daily. She had no recent medicine change prior to the eruption. Possible contact allergens were not applicable or relevant.

Physical examination revealed an impressive varicelliform dermatitis affecting the symmetric bilateral chest, abdomen, upper and lower back, buttocks, groin, thighs, upper arms, and tapering out onto the distal upper and lower extremities. She had subtle facial involvement, but her scalp, palms, soles, nails and mucous membranes were spared. There was no palpable lymphadenopathy.





The cutaneous lesions were numerous with multiple stages of evolution present, consisting of oval-shaped pink macules and papules, some with central dusky coloration and superficial scale (Figures 1a, 1b). Other lesions had eroded surfaces with hemorrhagic crusting (Figure 1c). The lesions were concentrated centrally, with relative sparing of acral sites, and tended to follow Langer's lines (Figure 1d), favoring an endogenous etiology. There were admixed hyper- and hypopigmented macules where previous lesions had resolved, yielding an overall mottled appearance. Our differential diagnosis at this point included PLEVA, lymphomatoid papulosis, erythema multiforme, drug eruption, varicella, and other viral exanthems.

Routine labs, including a complete blood count with differential and a complete metabolic panel, were unremarkable. Varicella zoster virus (VZV) antibody titers revealed negative immunoglobulin M (IgM) and elevated immunoglobulin G (IgG). Herpes simplex virus (HSV) IgG antibody titers were negative, but HSV IgM titers were positive. She denied any current or prior symptoms or signs consistent with oral or genital herpes simplex or zoster.

Histologic findings revealed a basket-weave orthokeratosis with focal parakeratosis and red-blood-cell exocytosis overlying diffuse basal vacuolization with underlying patchy lymphocytic infiltration, consistent with a diagnosis of PLEVA (Figure 2).

At that time, additional lab tests were performed in order to rule out possible underlying etiologies. The following were negative: anti-streptolysin O antibodies, western blot for HIV-1 and -2, rapid plasma reagin test, toxoplasma IgM and IgG antibodies, hepatitis C virus (HCV) antibody screen, hepatitis B virus (HBV) core and surface antibodies and surface antigen, and heterophile antibody test. Epstein-Barr virus (EBV) screening panel revealed positive nuclear antigen and viral capsid antigen IgG antibodies, but negative viral capsid antigen IgM and early antigen IgG.

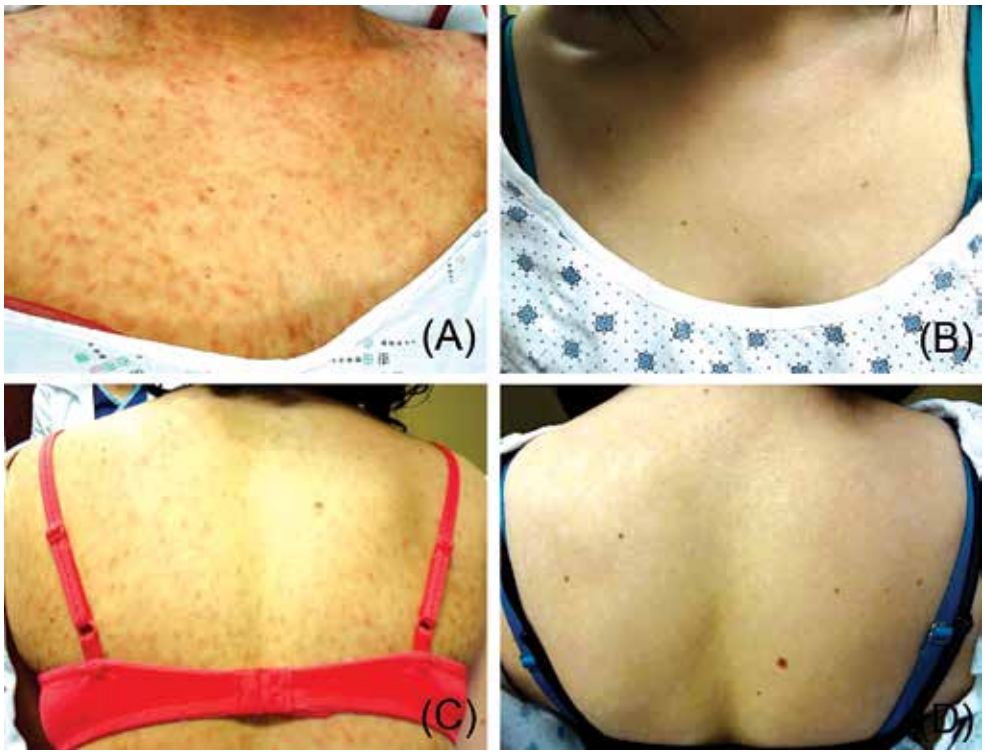
At her initial visit, we recommended completion of her course of doxycycline due to possible secondary infection. Triamcinolone 0.1% cream twice daily for two weeks, over-the-counter oral loratadine 10 mg twice daily, and over-the-counter oral diphenhydramine 25 mg at bedtime were prescribed for and provided symptomatic relief. After histologic confirmation of the diagnosis, we checked a beta human chorionic gonadotropin test, which was negative, and low-dose methotrexate was initiated at 7.5 mg weekly. Due to the presence of elevated HSV IgM antibodies, we recommended the patient complete a 10-day course of valacyclovir 1 gram twice daily, though the patient was still asymptomatic.

At one month follow-up, the patient reported no new lesions in the past two to three weeks, and the vast majority of the lesions were resolving with residual post-inflammatory hypopigmentation (Figure 3). The patient will be maintained on methotrexate 7.5 mg weekly until all lesions have resolved. The patient moved away, so HSV IgM and IgG labs were not repeated and there has been no long-term follow-up to date.

Discussion

Pityriasis lichenoides et varioliformis acuta (PLEVA), also known as Mucha-Habermann disease, is a rare disease on one side of a continuum with pityriasis lichenoides chronica (PLC), both in the family of clonal T-cell disorders.[1,2] Mucha first identified the acute form of pityriasis lichenoides in 1916. Habermann coined the phrase PLEVA in 1925.[3-6] The number of cases and the extent of PLEVA have not been well documented.[1] Incidence and prevalence seems to be increased in the fall and winter months, among males, and during the second and third decades of life.[7]

Though exact etiology is unknown, evidence suggests PLEVA is a T-cell dyscrasia or an immune-complex-mediated hypersensitivity reaction to an infectious agent or drug.[1] Postulated associations include: HIV, viral hepatitis, EBV, HSV, toxoplasma, TNF-a inhibitors, radiocontrast dyes, estrogen-progesterone, and



the measles vaccine.[2,8-12] While both PLEVA and PLC contain lesional T-cell infiltrates, $CD8^+$ cells predominate in PLEVA, and $CD4^+$ cells predominate in PLC.

The disease begins with an acute, diffuse eruption of erythematous macules and papules that rapidly evolve into crusted papules, vesicles, pustules and ulcers with various stages all present simultaneously.[13-16] Lesions are approximately 2 mm to 10 mm in diameter, arranged singly or in clusters, most commonly on the trunk, medial extremities, and flexor surfaces.[1,17] Patients with PLEVA are usually asymptomatic, but lesions may be pruritic or burn. While typically confined to the skin, patients may experience malaise, low-grade fever, lymphadenopathy, or rarely more serious complications like arthritis, superinfection, or bacteremia. A severe variant termed "febrile ulceronecrotic Mucha-Habermann disease" (FUMHD) may also involve the mucosa, gastrointestinal and pulmonary systems.[9] Lesions may spontaneously resolve within weeks to months, or follow a more unpredictable relapsing and remitting course. Residual varioliform scars and inflammatory hyper- or hypopigmentation may be seen.[1]

The differential diagnoses for PLEVA include: lymphomatoid papulosis, cutaneous small-vessel vasculitis, drug eruption, arthropod reaction, viral exanthems, folliculitis, erythema multiforme, and dermatitis herpetiformis.[1,17-21] Cutaneous biopsy is the gold-standard diagnostic test. Classic histologic findings of PLEVA are perivascular lymphocytic infiltrates, interface dermatitis with necrotic keratinocytes, and erythrocyte extravasation.[2] Other testing may be helpful in excluding alternate diagnoses and uncovering underlying etiologies, but are generally not necessary to diagnose PLEVA.

The majority of treatment options for PLEVA are based on uncontrolled trials, case reports, and anecdotes. Tetracycline in adults or erythromycin in children are prescribed first-line treatments for their anti-inflammatory properties, often requiring a prolonged course followed by a gradual taper.[2] Phototherapy is also effective, especially in relapsing disease, but the risk-benefit analysis of UV exposure is unclear.[17] Cases with a rapid onset may warrant low-dose weekly methotrexate. Combination therapy (e.g., erythromycin with psoralen + ultraviolet A phototherapy [PUVA] or methotrexate with PUVA) is also effective. Other antibiotics may be used for superinfection. Topical corticosteroids, topical coal tar, and systemic antihistamines have been used for symptomatic relief.[17] Systemic corticosteroids should be reserved for cases with systemic symptoms. Severe cases may require immune-suppressing and immune-modulating medications like tacrolimus and cyclosporine once infection has been excluded.[22] The prognosis for PLEVA is generally good. Patients with diffuse involvement typically experience resolution faster than those with localized involvement.[16] Pediatric patients are less likely to go into remission, are more likely to have permanent skin damage, and often do not respond to treatment as well as adults.[7] Predisposition toward developing T-cell lymphoma is controversial.[2]

A literature search revealed a very limited number of previous cases of PLC and FUMHC associated with HSV infection, but no cases of

HSV-associated PLEVA.[23,24] The connection between HSV and PLEVA was examined due to the obscurity of the association in the literature. In both cited case reports, the patients had active HSV lesions that coincided with their pityriasis lichenoides eruptions.[23,24] The active lesions tested positive for HSV.[23,24] Both cases were successfully treated with an antiviral (acyclovir).[23,24]

Conclusion

PLEVA is a rare disorder, usually self-limited, but carries an unpredictable course. It is grossly characterized by pleomorphic lesions at various stages of evolution, and histologically as an interface dermatitis consisting of $CD8^+$ T cells with extravasated erythrocytes. PLEVA has been associated with several infections and medications and has many proposed treatments. We report the case of a young, otherwise healthy adult female who was found to have a positive HSV IgM titer. This may or may not have been a coincidence, since repeat HSV studies were not done. Our patient was lost to follow-up, so there was no long-term surveillance for recurrence.

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Correspondence: Trey Haunson, DO; 1314 Fallsbrook Terrace; Acworth, GA 30101; 678-576-9316; thaunson@yahoo.com

Large Cerebriform Eccrine Porocarcinoma: A Case Report

Robert Lin, DO,* Alpesh Desai, DO, FAOCD**

*1st-year resident, South Texas Osteopathic Dermatology Residency Program, Houston, TX
**Program Director, South Texas Osteopathic Dermatology Residency Program, Houston, TX

Abstract

Porocarcinoma is a rare, slow-growing malignant neoplasm that may arise de novo or evolve from a pre-existing benign eccrine poroma. This lesion typically affects females over the age of 60 and represents about 0.005% of all cutaneous tumors. Porocarcinoma can be difficult to recognize. We present the case of a 46-year-old male with an unusually large, exophytic, cerebriform mass requiring multiple biopsies prior to a diagnosis of porocarcinoma.

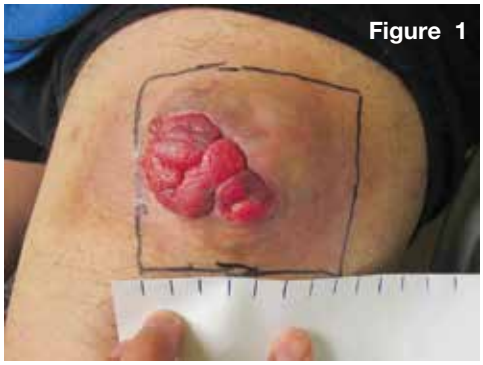


Figure 1

Introduction

Porocarcinoma is a rare, malignant tumor that develops from the intraepidermal ductal portion of the eccrine sweat gland. It first described by Pinkus and Mehregan in 1963 as an epidermotropic eccrine carcinoma.[1] With fewer than 250 cases reported worldwide in 2009, this condition accounts for about 0.005% of all cutaneous tumors.[2]

Affected individuals are typically elderly people over the age of 60, with a female predominance.[2-4] Lesions primarily appear on the lower extremities, though they can occur anywhere else on the body including the trunk, head, upper limbs, and neck.[3-6] Local and distant metastasis occurs in 10% to 20% of cases and often leads to poor prognostic outcomes, with a mortality rate of up to 80%.[3] A lack of specific clinical findings and the presence of benign poroid features make this condition difficult to diagnose. In the presence of a benign poroma, clinicians should always evaluate the likelihood of the lesion undergoing a malignant transformation in order to minimize the morbidity and mortality associated with this neoplasm.

Case Summary

A 46-year-old male presented with a large, slow-growing, non-painful, exophytic mass on the anterior aspect of his left thigh that had been present for more than 19 years. It had started as a small, 5 mm red papule and remained relatively small until about five years prior, when it began expanding in size and leaking clear fluid. Despite its unusual transformation, the lesion remained untreated due to the patient not having any health insurance.

Upon physical exam, the tumor was nodular, ulcerated, and cerebriform in appearance, measuring 7 cm x 6 cm (Figure 1). The tumor had restricted mobility in all directions, and its borders were poorly demarcated, with a bulk of the lesion buried deep in the dermis. General examination revealed no apparent signs of lymph-node involvement, and there were no other significant physical findings associated with this lesion.

A biopsy was performed with a generously wide shave of the ulcerating mass. However, despite the size of the sample provided, the lesion displayed mostly poroid cells with uniform nuclear features consistent with a poroid neoplasm (Figures 2-3).

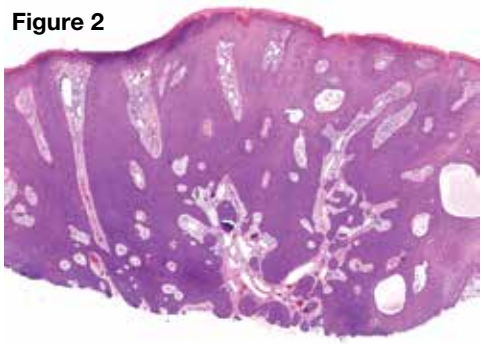


Figure 2

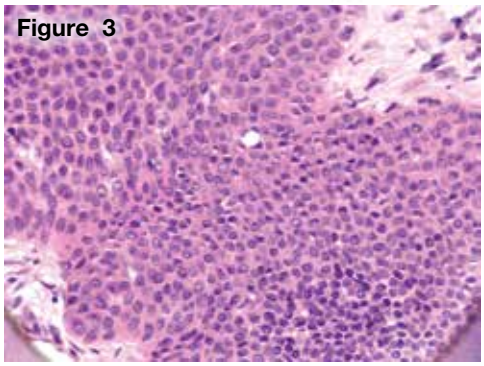
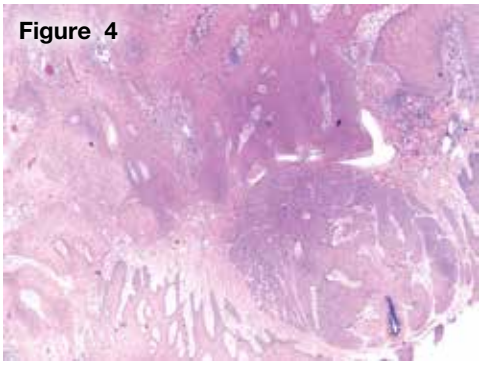


Figure 3

Due to the extensive involvement of the lesion and the lack of a firm diagnosis for a malignant finding, a second biopsy was performed with deeper samplings utilizing a punch instrument.

Review of the deeper sections of the second biopsy displayed a more infiltrative pattern with nuclear enlargement and mitotic activity (Figures 4-5). Even though the cytomorphology of the overall sample was uniform and lacked anaplastic features, there was enough evidence of cytological atypia and stromal infiltration at the base for it to be classified as a porocarcinoma (Figure 6).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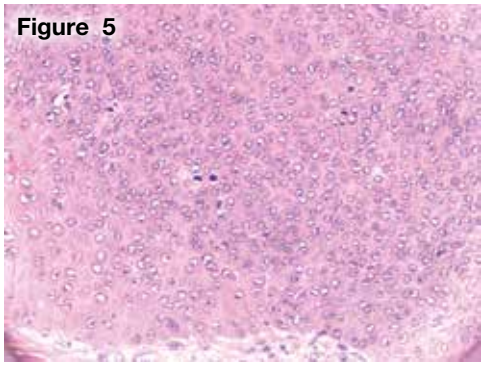
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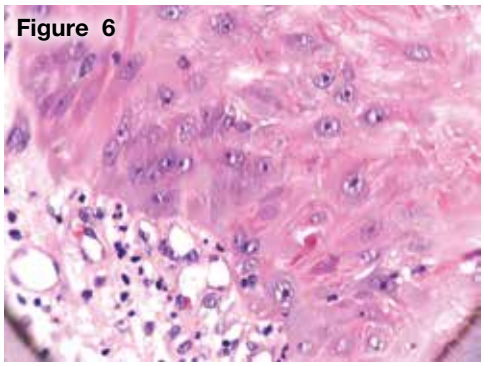
Figure 6

Due the unusually large size of the lesion and its poor prognostic features, the patient was referred to a general surgeon and an oncologist for further evaluation and treatment. The general surgeon performed a wide excision of the lesion followed by a left femoral lymphadenectomy of two nodes. The lesion was removed in its entirety, with the margins narrowly cleared on the deep surface by 3 mm. Both nodes removed from the left leg were negative for tumor.

As of this report, the surgical defect has been left open to heal by secondary intention with negative-pressure wound therapy in preparation for split-thickness skin grafting. Several radiologic and laboratory studies have also been performed and will be followed closely by the oncologist for any recurrence or metastasis.

Discussion

Establishing a solid diagnosis for porocarcinoma can be challenging. Unlike most malignant neoplasms, porocarcinomas have no specific clinical features and can vary in size, shape, and appearance.[3,4] Tumors may vary greatly in size, ranging from less than 1 cm to 10 cm.[3] Due to the condition's rarity and nonspecific appearance, a clinical diagnosis may never be accurate without proper histologic correlation, and it can easily be misdiagnosed as a squamous cell carcinoma, basal cell carcinoma, seborrheic keratosis, or metastatic adenocarcinoma.[2,3]

Although porocarcinomas have no specific clinical features to identify, the sudden transformation of any lesion, becoming nodular, infiltrative, ulcerated, or polypoid, is often indicative of an underlying malignant process.[3] Since porocarcinomas have been known to develop both de novo and from benign poromas, diagnosis of this condition can take many years depending on when the lesion underwent malignant transformation.[2,4] As a result, it is common to find porocarcinomas arising from adjacent poromas histologically.[6,7] The pathogenesis and neoplastic behavior of this condition explains why the biopsy samples taken from our patient displayed the cytologic uniformity of a benign process rather than a malignant one.

The classic histopathologic features of porocarcinomas typically involve intra-epidermal and dermal nests with features of cellular atypia and increased mitotic activity. These tumor masses form clearly demarcated nests of polygonal cells with hyperchromatic irregular nuclei, prominent nucleoli, and scant eosinophilic cytoplasm.[7,8] Immunohistochemical staining techniques may be used to aid in the diagnosis of porocarcinoma, but results can vary depending on the histologic presentation of the lesion. Two of the main markers for this condition include epithelial membrane antigen (EMA) positivity and carcinoembryonic antigen (CEA) negativity. However, CEA staining for the evaluation of porocarcinoma can be misleading because it displays positive markers in tumors containing well-formed ducts, which are often found in significant portions of the lesion.[9]

Many histologic features of porocarcinoma have proved helpful in assessing prognosis. The presence of lymphovascular invasion, a tumoral depth greater than 7 mm, and a mitotic index of more than 14 mitotic cells often indicate a worse prognosis compared to cases without these particular findings.[10,11] Local and regional lymph-node metastases are observed in approximately 20% of patients, and distant metastases to the viscera and bone arise in 10% of patients with this condition.[12] Prognoses of patients with metastatic porocarcinomas are usually poor, with a mortality rate of up to 80%.[13]

Due to the rarity of this condition and the subsequent lack of opportunities to evaluate new treatment options, surgical excision of the primary lesion continues to be the treatment of choice, with a cure rate of up to 80% and a recurrence rate of less than 20%.[2-4] Any evidence of local or distant metastatic involvement would warrant regional lymph-node dissection in addition to close follow-up with an oncologist.[10] Postoperative radiation or chemotherapeutic agents have been shown to improve patient outcomes and reduce the likelihood of recurrence.[14] Mohs micrographic surgery is another viable treatment option and has been shown to produce moderate success without recurrence at two years to four years postoperative follow-up.[15] However, if patients have multiple metastatic lesions or are poor surgical candidates, chemotherapeutic agents such as tamoxifen and docetaxel can provide effective, systemic alternatives to surgery.[16]

Conclusion

Definitive diagnosis of porocarcinoma requires the collaboration of expert pathologic and oncologic studies. The case presented here shows that clinical findings are just as important as histological findings in diagnosing a suspected porocarcinoma. Upon receiving a diagnosis of benign poroma, every clinician should reevaluate the lesion in terms of its likelihood to undergo a malignant transformation. Early intervention can help minimize the morbidity and mortality of this potentially dangerous neoplasm.

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Correspondence: Robert Lin, DO; 2120 Ashland St., Houston, TX 77008; Ph: 713-864-2659; Fax: 713-864-5577; Dr.RobertLin@gmail.com

An Unusual Clinical Presentation of Palisaded Neutrophilic and Granulomatous Dermatitis

Marina Matatova, DO
Dermatology Resident, 2nd Year, St. John's Episcopal Hospital-Dermatology Residency Program, Far Rockaway, NY

Abstract

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is thought to be an uncommon cutaneous manifestation associated with rheumatoid arthritis as well as connective-tissue, lymphoproliferative, and immune-complex diseases. We present a PNGD patient with the unusual clinical presentation of a unilateral, asymptomatic lesion. Although work-up of this patient was negative, PNGD may be the initial presenting symptom of corresponding disease, so diagnosis of PNGD should warrant work-up for underlying pathologies.

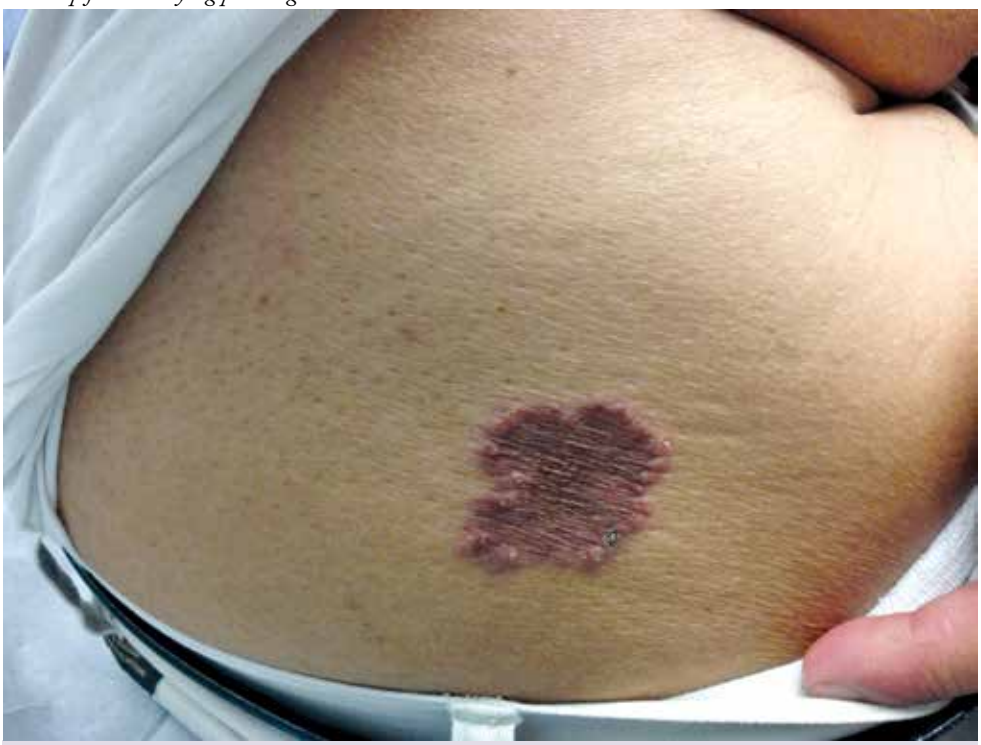


Figure 1: On right lateral upper leg, a 3.1 cm x 3.4 cm, clover-shaped, violaceous plaque with pink-to-waxy papules at the peripheral border.

Introduction

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is believed to be a rare cutaneous manifestation of connective-tissue, lymphoproliferative, and immune-complex diseases, rheumatoid arthritis (RA), and medication use.[1,2] It most commonly presents as symmetric, skin-colored to erythematous papules and nodules located on the extremities, particularly on the extensor surfaces. The lesions may be asymptomatic, pruritic, or painful. On histopathology, early lesions of PNGD exhibit leukocytoclastic vasculitis with significant neutrophilic infiltrate and collagen degeneration, with mature lesions showing palisaded granulomas surrounding fibrin deposition, necrosis and nuclear debris. Management of PNGD includes high-potency topical or intralesional corticosteroids and/or discontinuation of the offending agent.

Case Presentation

A 69-year-old Pakistani male presented to a dermatology office with a chief complaint of a six-month history of a lesion on his right hip. The patient denied any pain or itch associated with the lesion, as well as any previous biopsies or treatment of the lesion. The only past medical history the patient reported was diabetes mellitus type II, for which he was taking metformin. The only other oral medication the patient took was a multivitamin. He denied any family history of skin disorders, any surgical history, and any known allergies. On physical exam, on the right lateral upper leg there was a 3.1 cm x 3.4 cm, clover-shaped, violaceous plaque with pink-to-waxy papules at the peripheral border (Fig. 1). No other skin lesions were noted on exam. On review of systems, the patient denied any joint disease or discomfort.

A 3 mm punch biopsy was performed at the initial visit, which revealed a superficial and deep, perivascular and interstitial infiltrate of lymphocytes, histiocytes, numerous eosinophils and neutrophils, with a foci of basophilic

Figure 2a

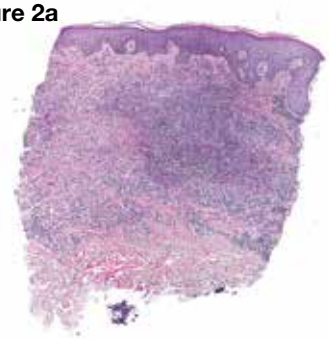


Figure 2b

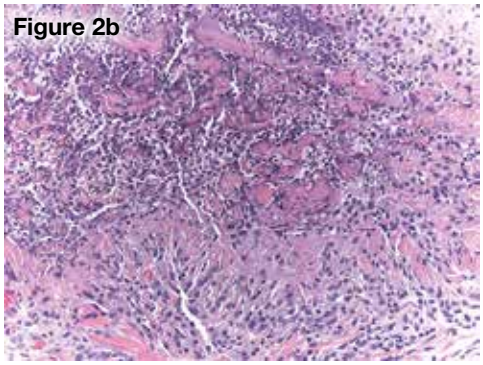
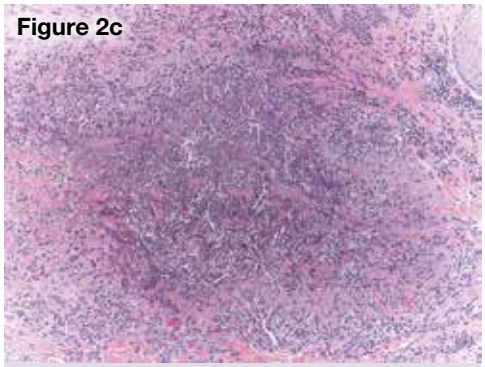


Figure 2c



Figures 2a-2c: Superficial and deep, perivascular and interstitial infiltrate of lymphocytes, histiocytes, numerous eosinophils and neutrophils, with a foci of basophilic collagen degeneration surrounded by numerous eosinophils. (2b, 2c: Higher-power views.)

collagen degeneration surrounded by numerous eosinophils (Fig. 2a-c). The diagnosis of palisaded neutrophilic and granulomatous dermatitis was made.

The patient was evaluated for any underlying conditions by numerous labs, which were all within normal range except for an elevated HgA1C. These labs included ANA, RPR, RF, anti-dsDNA, anti-Smith Abs, hepatitis profile, LHD, ESR, and C-reactive protein. The patient was placed on topical class I corticosteroid with mild improvement of the lesion.

The plan of treatment for this patient is possible intralesional steroid, oral corticosteroid, and possible re-biopsy if the lesion worsens. He will also be monitored for development of any underlying systemic disease.

Discussion

Dykman et al. first described palisaded neutrophilic and granulomatous dermatitis (PNGD) in 1965, in two patients with rheumatoid arthritis presenting with linear subcutaneous bands on the trunk.[3] Since then, there have been more case reports of similar lesions, which have been given multiple names. PNGD has been described as an atypical, GA-like tissue reaction; rheumatoid papules; Churg-Strauss granulomas; superficial ulcerating rheumatoid necrobiosis; and interstitial granulomatous dermatitis with cutaneous cords and arthritis (Ackerman syndrome).[4,5,6] In 1994, Chu et al. evaluated nine patients with PNGD and subsequently proposed that histopathologically, PNGD displays a spectrum of various characteristics depending on the duration of the lesion.[7] They also coined the term "palisaded neutrophilic and granulomatous dermatitis," encompassing previously reported similar cases under the umbrella term of PNGD.[8]

Clinically, PNGD has various presenting characteristics. Early lesions of PNGD may appear as urticarial-like annular plaques or may even have a livedoid appearance. With time, the lesions may become more infiltrative and pleomorphic, presenting as violaceous, annular plaques, waxy papules, painful subcutaneous nodules or indurated linear bands.[5] Some lesions may also be asymptomatic. The eruption of PNGD is symmetrically distributed on the trunk and extensor surfaces of the upper limbs. Patients with PNGD have also been reported to develop symmetric polyarthritis.[8] In the patient described herein, PNGD presented as a solitary, asymmetric, asymptomatic lesion on the lateral upper leg.

Many theories have been proposed regarding the pathogenesis of PNGD. Presence of IgM and C3 within the small vessels of PNGD lesions suggest possible precipitated immune complexes generated by underlying systemic disease.[3,9] High titers of antineutrophilic antibody (ANA), anti-dsDNA and rheumatoid factor (RF) have been correlated with this cutaneous eruption and consequent worsening of the systemic disease.[3,10] The deposition of immune complexes within the dermal vessels triggers activation of the complement and neutrophils, which leads to ischemia and degenerated collagen, followed by a granulomatous reaction to the degenerated collagen.[9,11]

A literature review revealed cases of PNGD associated with multiple drug therapies, especially TNF-alpha inhibitors used in patients with rheumatoid arthritis. More specifically, the agents most commonly responsible for the eruption are infliximab, etanercept, adalimumab, and lenalidomide.[5] The exact mechanism of PNGD induction by anti-TNF-alpha medications is not well understood. However, it has been postulated that TNF-alpha inhibitors induce leukocytoclastic vasculitis via production of autoantibodies, which bind to rheumatoid factor (RF) IgM/C3 and cause a precipitation of these immune complexes within vessels, followed by a chain of events that leads to granulomatous inflammation.[5] Patients with RA tend to develop lesions such as PNGD and rheumatoid nodules, which are both granulomatous reactions. It has also been noted that treatment of RA patients has resulted in accelerated formation of pulmonary granulomatous inflammation. Furthermore, TH1 predominance in RF leads to an increased TNF-alpha microenvironment and an increased influx of macrophages in response to the leukocytoclasis triggered by TNF-alpha inhibitors.[5]

The onset of PNGD lesions associated with anti-TNF-alpha agents may vary from one month to two years.[5] Cessation of the offending medication usually results in improvement and at times clearing of the lesions. Other oral medications cited in the literature as associated with PNGD eruption include methotrexate, leflunomide, azathioprine, calcium-channel blockers, beta-blockers, lipid-lowering agents, antihistamines, anticonvulsants and antidepressants.[1,5]

Histopathologically, PNGD may exhibit pleomorphic changes. PNGD represents a continuum, with early lesions exhibiting diffuse interstitial inflammation composed of lymphocytes, histiocytes, eosinophils and few neutrophils, and late lesions maturing into a palisaded granuloma surrounded by dense histiocytic and neutrophilic infiltrates with central degenerated collagen and leukocytoclastic debris.[7] According to Chu et al., the spectrum of PNGD is merely a progression of immune-complex-mediated changes from leukocytoclastic vasculitis (LCV) in early lesions to palisaded granulomas in fully developed lesions, followed by an end-stage of fibrosis. A common histological hallmark of all PNGD lesions is a palisaded arrangement of cells.[7] The biopsy of the lesion described here revealed a superficial and deep, perivascular and interstitial infiltrate of lymphocytes, histiocytes, numerous eosinophils and neutrophils, with a foci of basophilic collagen degeneration surrounded by numerous eosinophils. These changes may represent an intermediate lesion, and the six-month history of the lesion noted by the patient supports these findings.

It is important to note that both clinically and histologically, PNGD may resemble granuloma annulare. However, PNGD exhibits a granulomatous inflammation in the lower half of the reticular dermis, described as "bottom-heavy," while in granuloma annulare it is more concentrated in the papillary dermis, or "top-heavy."[1,9]

The clinical course of PNGD lesions is usually self-limited and may resolve spontaneously. It has been reported that patients with PNGD may develop symmetric polyarthritis. Management of PNGD consists of topical corticosteroids, tacrolimus, low-dose oral corticosteroids, dapsone, colchicine, cyclosporine, cyclophosphamide, mycophenolate mofetil and hydroxychloroquine.[9,11] Lesions of PNGD tend to recur once therapy is discontinued.

Conclusion

Although the patient in this case was not diagnosed with an underlying immune-complex disorder, recognition of PNGD lesions is of importance as it may lead to an early diagnosis of an underlying systemic disease. PNGD presents with a spectrum of lesions, both clinically and histologically, and undergoes an evolutionary process. Thus, a high index of suspicion may result in early diagnosis and management of many systemic conditions. The patient in this case report should be periodically evaluated for development of an immune-complex disease.

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Correspondence: Marina Matatova, DO; Department of Dermatology, 327 Beach 19th St., Far Rockaway, NY 11691; mmatatova@aol.com.

Scleredema Diabeticorum: A Case Report and Review of Literature

Donna Tran, DO,* Navid Nami, DO**

*Dermatology Resident, PGY2, Western University of Health Sciences, College Medical Center, Long Beach, CA
**Program Director, Dermatology Residency, Western University of Health Sciences, College Medical Center, Long Beach, CA

Abstract

Scleredema is a rare connective-tissue disorder characterized by diffuse, non-pitting induration of the skin. Scleredema is divided into three types, distinguished by their associations with infection, monoclonal gammopathy, and diabetes mellitus (scleredema diabeticorum). Pathogenesis is largely unknown. We present a case of a 65-year-old man with scleredema diabeticorum and review the literature and treatment modalities.

Introduction

Scleredema, originally described by Buschke in 1902, is an uncommon, fibromucinous connective-tissue disorder characterized by symmetrical, diffuse induration of the skin due to accumulation of collagen and aminoglycans in the dermis.[1] Hands and feet are characteristically spared.[2] Cardiac and other organ involvement is rare, but in severe cases, patients may present with restrictive lung disease.[3,4] Classically, three variants of scleredema have been described, one associated with infection (usually streptococcal), one with monoclonal gammopathy, and one with diabetes mellitus. We present a case of a 65-year-old male with insulin-dependent diabetes mellitus who presented with a progressive history of thickening of the skin on his back.

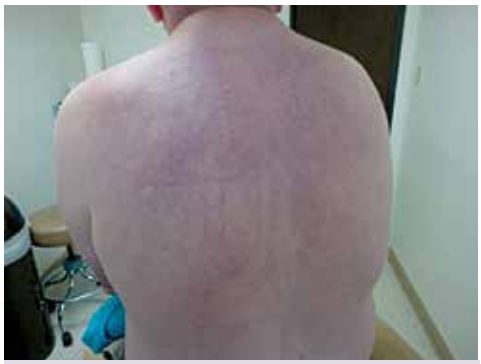

Figure 1. Thickening and erythematous induration of the posterior neck and upper back.

Case Report

A 65-year-old man presented with complaints of painless, progressive hardening of his upper back present for years. He denied any associated symptoms. Past medical history was significant for insulin-dependent diabetes mellitus. Physical examination revealed a symmetrical, erythematous, indurated plaque with indistinct borders involving his posterior neck and upper back (Figure 1). No restriction in range of motion of the shoulders and neck was noted.

A histopathologic examination of a punch-biopsy specimen from the skin on his back revealed an intact epidermis with no interface changes. A scant superficial perivascular lymphocytic infiltrate was present (Figure 2). A colloidal-iron stain revealed an increase in dermal mucin (Figure 3). These features supported the diagnosis of scleredema diabeticorum. Our patient was asymptomatic and described no restriction in movement. To our knowledge, his diabetes mellitus was controlled with subcutaneous insulin injections and diet. He opted for close follow-up.

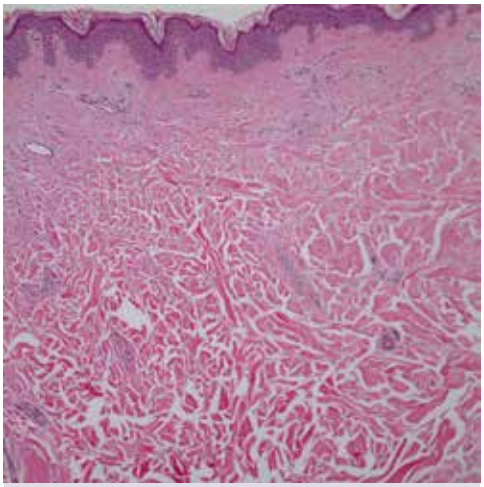

Figure 2. Scant superficial perivascular and lymphocytic infiltrate with sparing of the epidermis.

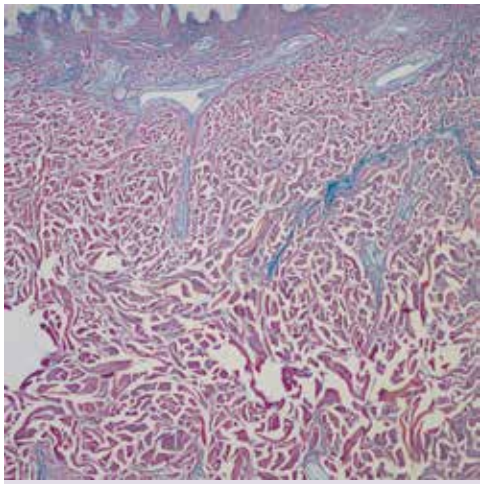

Figure 3. Colloidal-iron positive with increase in dermal mucin.

Discussion

Scleredema is a sclerotic skin disease that is divided into three types. Type 1 typically affects middle-aged women and is often preceded by an acute febrile disease, most commonly of streptococcus origin. A sudden-onset hardening of the skin of the cervicofacial region with spontaneous resolution in a period of months to years is seen. Type 2 scleredema appears in individuals without diabetes or infection. This type occurs in women and has an insidious and prolonged course. Monoclonal gammopathy, most commonly IgG, with progression to multiple myeloma may be seen.[5,6] Type 3 occurs primarily in obese, middle-aged men with a long history of diabetes mellitus, as seen in the patient described here.[3] This third type may be referred to as "scleredema diabeticorum."

Onset of scleredema diabeticorum is insidious, and a progressive, non-pitting induration of the skin involving the posterior neck, back, and shoulders, and less commonly arms, is often seen.[3] Erythema and a peau d'orange appearance may be present, with indistinct demarcation between normal and abnormal skin. Individuals often have a long history of poor metabolic control as well as diabetic complications; however, cases of scleredema diabeticorum in diabetics with controlled glucose have been reported.[7]

The pathogenesis of scleredema diabeticorum is uncertain. Various etiologies have been proposed, including irreversible glycosylation of collagen and resistance to degradation by collagenase, leading to collagen accumulation.[8] Other hypotheses suggest microvascular damage and hypoxia stimulating mucin and collagen synthesis.[9]

Diagnosis of scleredema is based on clinical findings of non-pitting induration or stiffness of the skin, which may be of sudden or insidious onset. Histopathologic confirmation is not required. On skin biopsy, the epidermis is usually spared. Thickened collagen bundles within the reticular dermis separated by mucin-containing fenestrations is characteristic. No increase in number of fibroblasts is seen.

Scleredema may be confused with scleroderma, but absence of a history of Raynaud's phenomenon, calcification, or telangiectasia points to scleredema. Scleromyxedema, a generalized primary cutaneous mucinosis that also may have associated monoclonal gammopathy, can be differentiated from scleredema by its diffuse, waxy papules, often in a linear array, in addition to the proliferation of fibroblasts seen histologically.

Scleredema diabeticorum is a relatively underestimated and unrecognized complication of diabetes. The exact prevalence is not known. Cole et al. observed a prevalence of 2.5% in a population of 424 diabetic patients.[10] Satter et al. found a higher prevalence of 14% in a population of 100 hospital-based patients with diabetes mellitus.[11] In most cases, glucose control is the first recommended step in management. In one series of four patients with type 1 diabetes, implantable insulin pump therapy led to improvement of glucose control as well as clinical improvement of the skin in terms of redness, swelling, and induration.[12] Unlike streptococcal-associated scleredema, which often carries a better prognosis and resolution of skin disease after a period of months to years, scleredema diabeticorum often follows an indolent course, and lesions may persist despite good metabolic control.[17] For most patients, diabetes-associated scleredema is a relatively mild disorder, although rarely death may occur when internal organs are involved.[13]

Multiple treatment modalities have been reported as case reports or small series with variable success, including corticosteroids, cyclosporine,[14] methotrexate,[15] potassium para-aminobenzoate,[16] and electron-beam radiation therapy.[4] In a few reported cases, tamoxifen has been effective in improving skin thickening and joint mobility within months of starting treatment.[17] More recently, ultraviolet A-1 phototherapy and psoralen with ultraviolet A (PUVA) has been effective in patients with scleredema diabeticorum.[7] The mechanism of benefit of PUVA on scleredema is suggested to be an increase in collagenase synthesis by fibroblasts and the inhibition of de novo type 1 collagen synthesis.[7] In one case, combining local PUVA and colchicine was reported to have a synergistic benefit in the treatment of scleredema diabeticorum in a 53-year-old woman.[18] At the end of treatment, the patient was able to lie in a supine position without pain or paresthesia, and her epidermal thickness, measured with a 17-MHz probe ultrasound, was decreased by 34.29%, with dermal thickness decreased by 7.03%.[18]

Conclusion

The frequency of scleredema diabeticorum is underestimated. In most cases, scleredema diabeticorum is a self-limited, benign condition. However, severe cases with rapid progression and disabling consequences may occur. Improvement of diabetes control is first-line treatment. Our patient was asymptomatic and opted for close follow-up. His diabetes was controlled with diet management, exercise, and insulin subcutaneous injections.

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Correspondence: Donna Tran, DO; DonnaDTran@gmail.com

The bug beneath the bathing suit: A case report and discussion of seabather's eruption versus cutaneous larva migrans

Andrew Jensen, BS,* Marcus Goodman, DO, FAOCD**

*Medical Student, 4th year, Philadelphia College of Osteopathic Medicine - Georgia Campus, Suwanee, GA
**Dermatology Residency Program Director, PCOM/North Fulton Hospital Medical Campus, Roswell, GA

Abstract

Seabather's eruption is an important differential diagnosis when a patient who has recently swum in a subtropical ocean presents with a pruritic rash in the distribution of their swimwear. Treatment with systemic corticosteroids is indicated in severe cases and can successfully reduce symptoms. Oral steroid therapy in general has proven to be an effective treatment for many acute and chronic diseases but has long been associated with increased risk for infections. In this report, we present an atypical case of cutaneous larva migrans and discuss its clinical unmasking after systemic steroid treatment was given for an initial diagnosis of seabather's eruption.

Introduction

Seabather's eruption is a benign, superficial reaction to toxins from marine-animal larvae. It is the most common marine-related problem in the waters south of the United States.[1] It was reported in Florida as early as 1903 as a "rash which set up an intense itching" shortly after bathing in ocean water.[2] In 1949, Sams postulated the eruption was caused by "some living, microorganism, in the nature of nematocysts from some form of coelenterate which is free floating."[3] Substantiating Sams' initial claim, the thimble jellyfish, Linuche unguiculata, is now thought to be the cause of seabather's eruption in the southeastern United States, Mexico and the Caribbean.[4] The skin reaction occurs when jellyfish stinging cells called nematocysts get trapped underneath swimwear and inject venom there, causing an immune response and succeeding rash. The condition is often exacerbated with persistent use of the contaminated swimwear, causing friction on nematocysts, or when the swimmer later bathes in fresh water, inducing osmotic irritation and subsequent envenomation.[5]

Seabather's eruption is diagnosed clinically as a constant, pruritic and erythematous rash, papular, macular or urticarial, most commonly located underneath swimwear. Differential diagnoses include animal schistosomiasis (swimmer's itch), scabies, insect bites, varicella zoster, contact dermatitis, folliculitis and almost any marine-origin dermatosis. A skin biopsy is not required for diagnosis of seabather's eruption but most commonly shows a superficial and deep perivascular and interstitial infiltrate consisting of lymphocytes, neutrophils, and eosinophils.[6] The syndrome is not considered contagious and is self-limiting, usually lasting an average of three to seven days. Treatment of seabather's eruption consists mainly of supportive therapy with topical corticosteroids and antihistamines, with systemic steroid use reserved for severe cases.

Case Report

A 52-year-old female presented to her dermatologist complaining of an itchy rash on her groin and upper leg for one week. The patient stated she recently traveled to Mexico, where she spent several days on the beach and swimming in the ocean. Physical exam revealed erythematous, edematous papules on her lower abdomen and groin, assuming a location directly beneath her swimsuit (Figure 1). A biopsy was collected, and the patient was discharged with a topical corticosteroid and antihistamine regimen.

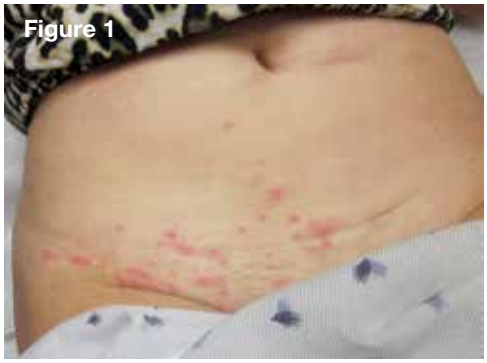
Figure 1

Less than 24 hours after the initial visit, the patient called the office complaining she could not tolerate the constant itch. She was prescribed a methylprednisolone dose pack and was encouraged to follow up with the office in four to five days or earlier if symptoms worsen. Biopsy results were received (Figures 2 and 3) and revealed a "papular urticaria/arthropod assault" consistent with an initial clinical diagnosis of seabather's eruption.

Five days after the initial visit, the patient returned for follow-up stating the rash was spreading. Physical exam showed a worsening of symptoms with urticarial papules and serpiginous plaques radiating from the initial site (Figure 4). The patient was diagnosed with cutaneous larva migrans. She was instructed to discontinue the oral steroid and was given a single dose of 12 mg oral ivermectin. One week after treatment, the patient's rash was resolved.

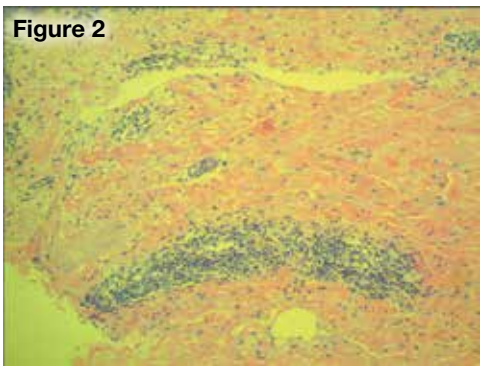
Figure 2

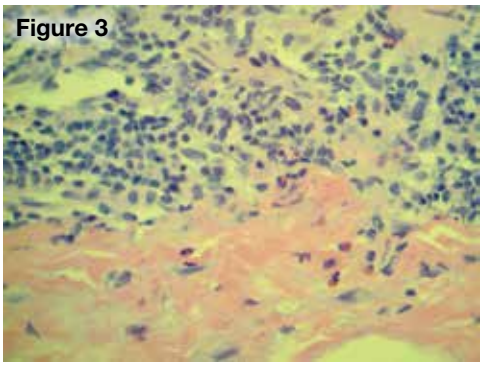
Figure 3


Figure 4

Discussion

Corticosteroids and immune function

Corticosteroids play a critical role in treating common diseases like rheumatoid arthritis, chronic obstructive pulmonary disease and a host of mild-to-severe inflammatory disorders. Since their advent in the late 1940s, both short- and long-term use of oral corticosteroid therapy has

been associated with increased risk of infections.[7] The mechanism of action of these biologically active steroid hormones is spread across the entire immunological-response spectrum. Lionakis reported that glucocorticoids affect virtually every cell type involved in immunity and inflammation.[8] Klein observed that a single dose of corticosteroids caused neutrophilic leukocytosis, monocytopenia, and eosinopenia within four to six hours of dosing.[9] These and other reports have shown that steroid therapy is associated with decreased migration of neutrophils to target tissues, a reduction of inflammatory cytokines, and an inhibition of hydrogen peroxide production in lysosomes.[8-10] Together, these inhibitions decrease microorganism killing and subsequent infection elimination.

Cutaneous larva migrans

Cutaneous larva migrans (CLM), or creeping eruption, is the most common skin disease among travelers returning from tropical destinations.[11] CLM is caused by a penetrating parasite, most commonly the Ancylostoma braziliense, which flourishes in the gastrointestinal tracts of cats and dogs. Commonly found along tropical beaches where animal feces gets deposited, parasite larvae can remain viable and infectious for months in a warm and humid environment.[12] With 95% of patients with CLM reporting recent exposure to a beach, prevention is focused on limiting contact with feces-contaminated sand or soil.[1] The best suggested community prevention of CLM has been to ban dogs from beaches, a difficult task especially in developing countries. More individual forms of prevention include wearing shoes while walking, and lying on a mattress or sand washed with the ocean tide when touring a beach frequented by dogs.

In a human host, larvae migration is confined within the epidermis, causing the classic presentation of incessantly pruritic, erythematous, edematous, serpiginous tracks.[13] The irregular track pattern advances at an average rate of 2.7 millimeters per day and can often be used to estimate infection duration.[12] CLM is diagnosed clinically by recognition of these raised, red-purple, linear or serpiginous tracks, which usually occur along the feet. Other common sites of involvement include the buttocks, thighs, elbows, back and face.

For many clinicians, the disease may mimic scabies, schistosomiasis, tinea corporis, or contact dermatitis. But as outlined by Heukelbach, these can be easily ruled out once features of CLM are understood, leaving a differential diagnosis comprising dermatoses with serpiginous, migratory lesions.[14] These can include strongyloides stercoralis (larva currens), fascioliasis, varicella zoster, a serpiginous ganglion cyst, and hair growing horizontally in the skin. Skin biopsy is not recommended for diagnosis of CLM, as larvae advance ahead of the visible tracks, usually resulting in a negative biopsy. Eosinophilia is present in only 30% of cases, proving this test to be inadequate as a diagnostic study.[12] First-line treatments of CLM include oral ivermectin and albendazole. Caumes reported that a single 12 mg oral dose of ivermectin achieved a cure rate of 81% to 100%, and a single 400 mg oral dose of albendazole achieved a cure rate of 46% to 100%.[11] Oral steroids are generally avoided in parasitic or other occult infections due to their immunosuppressing effects.

Conclusion

As discussed in this case report, we submit that our patient had an atypical presentation of cutaneous larva migrans most likely from lying on a sandy beach contaminated with dog feces. With the original erythematous, papular rash appearing directly beneath the patient's swimwear and the absence of any cutaneous tracks, seabather's eruption was initially diagnosed. Not until treatment of a severely pruritic eruption with an oral steroid regimen did identifiable serpiginous and linear tracks appear, warranting a modification of the clinical diagnosis and treatment. Once therapy was changed to an indicated treatment of cutaneous larva migrans, the patient's symptoms resolved.

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Correspondence: Marcus Goodman, DO; goodmandermatology@gmail.com

Segmental Neurofibromatosis: A Report of Two Cases and Review of a Rare and Inconspicuous Subset of a Common Genodermatosis

Sarah Ferrer-Bruker, DO,* Christina Steinmetz, DO,** Brent Schillinger, MD,*** Andleeb Usmani, DO****

*Second-year Dermatology Resident, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL
**Third-year Internal Medicine Resident, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL
***General Dermatology Attending, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL; Palm Beach Dermatology Associates, Delray Beach, FL
****General Dermatology Attending, Palm Beach Consortium for Graduate Medical Education, West Palm Hospital, West Palm Beach, FL; TruDerm, Wellington, FL

Abstract

Segmental neurofibromatosis is an infrequent and underdiagnosed subset of the neurofibromatosis (NF) spectrum. It is the localized form of the disease. Although quite subtle, less severe, and variable in presentation compared to classic NF, similarities regarding risk of malignancy, ophthalmologic findings, and potential genetic transmission have been reported. In this article, we present two cases of segmental neurofibromatosis and review the spectrum of clinical presentations, historical classifications, genetics, and potential clinical implications of the disease.

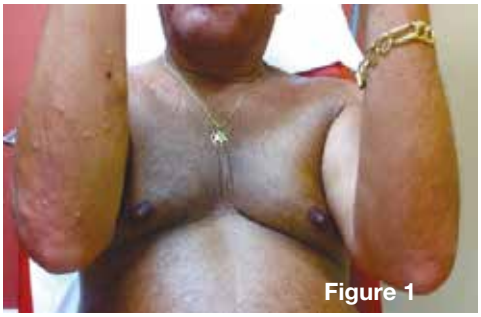


Figure 1

Introduction

The neurofibromatoses, which consist of a heterogeneous group of inherited disorders affecting the skin and central nervous system, affect over 2 million people worldwide, including over 100,000 Americans.[1] Popular film and fictional literature have depicted the debilitating disease with characters such as Quasimoto in Victor Hugo's "The Hunchback of Notre Dame." In 1642, it appeared in an atlas called Monstrorum Historia.[2] There are three large categories of neurofibromatosis (NF), which are presently classified according to their molecular aspects: NF Type 1, first described by von Recklinghausen in 1882, which is the most common form; NF Type 2, with the hallmark feature of bilateral vestibular neuromas; and finally all other types of NF, which includes atypical or variant forms of the disease.[3,4] Segmental neurofibromatosis falls into the latter category and is easy to miss due to its uncommon characteristics. Failure to accurately diagnose the disease can lead to negative patient outcomes. In this case series, we attempt to shed light on the condition and guide practitioners in caring for this group of patients who may be easily overlooked

Case 1

A 66-year-old Caucasian man presented to our dermatology clinic with complaints of "painless bumps" on the dorsal aspect of his right forearm. They were present since puberty, but in the last few years the patient noticed them enlarging and increasing in number. He denied any pain or discomfort or any other significant dermatologic history. He relayed a medical history significant for a meningioma incidentally found on a CT scan on a hospital admission for transient ischemic-attack-type symptoms, as well as a history of a gastric MALT lymphoma treated with radiation therapy 15 years prior. He followed up regularly with a primary care doctor and subspecialists and was up to date with age-appropriate cancer screenings and ophthalmologic exams, which were all negative. He had no family history of neurofibromatosis. He had no children.

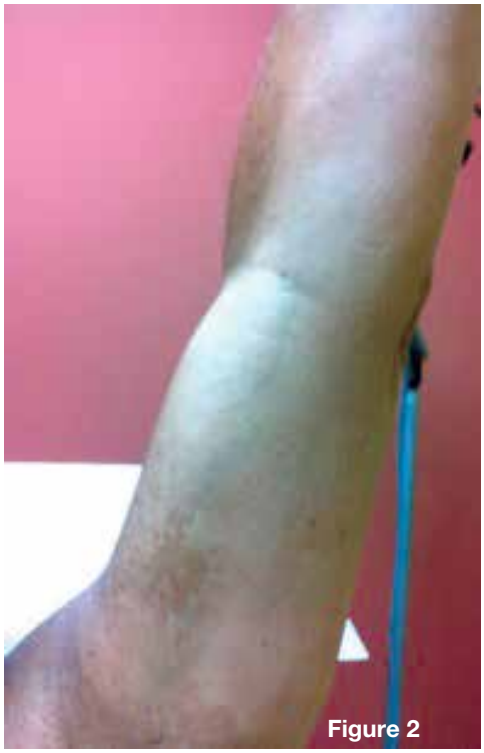


Figure 2

Physical examination revealed greater than 15 soft, flesh-colored nodules and tumors varying in size in a dermatomal distribution on the dorsal aspect of the mid to proximal right forearm (Figure 1). Incidentally, on the left inner proximal arm superior to the axilla there was a café au lait macule with associated surrounding freckling (Figure 2).

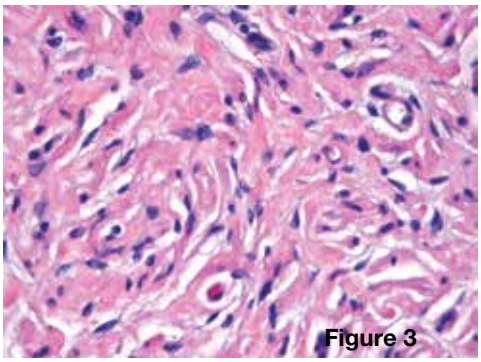


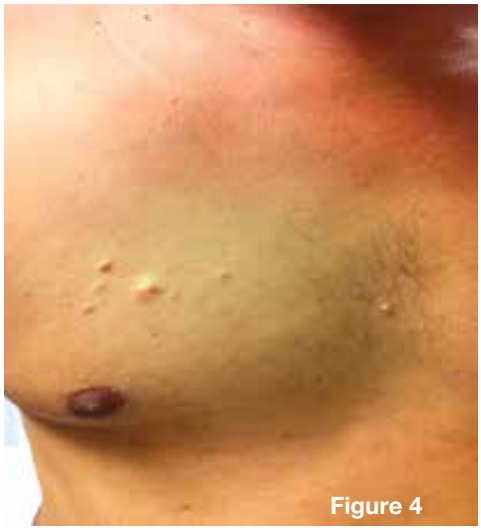
Figure 3

Incisional biopsy of one flesh-colored nodule on the right forearm demonstrated well-circumscribed areas of pale, spindled cell proliferation characterized by wavy fibrils with elongated nuclei and scattered mast cells (Figure 3). The biopsy was negative for Melan-A and positive for S-100 protein, consistent with neurofibroma.

Case 2

A 39-year-old Puerto Rican male presented to our dermatology clinic with history of an increasing number of pink- to flesh-colored, rubbery papules on his right chest, side, and back. Present since his teenage years, they were non-tender and occasionally pruritic. He had no significant medical history besides head trauma requiring surgery at age 6. However, he denied regular follow-up with a physician. He denied family history of neurofibromatosis. He had five children, all of whom so far appeared to be unaffected.

Physical exam revealed greater than 10 firm-to-rubbery, pink- to flesh-colored papules in a dermatomal distribution extending from the



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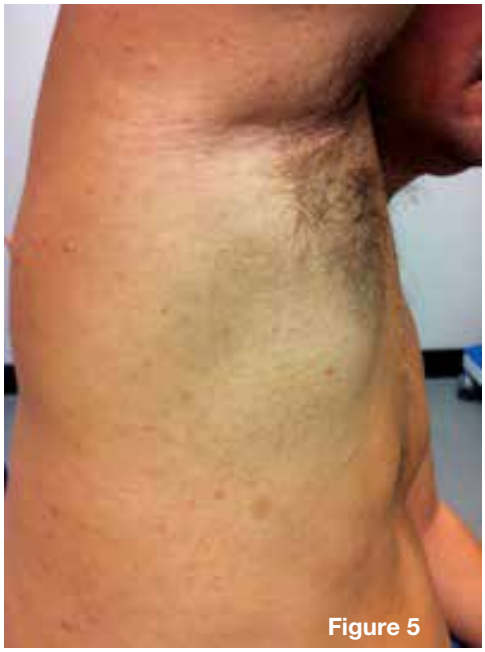

Figure 5

anterior right chest and wrapping around to the right mid-thoracic region. Also present on the right side were several tan macules in the axillary region (Figures 4 and 5).

Shave biopsy of one of the papules of his right chest revealed a dermal proliferation of delicate spindled cells within a stroma of wavy collagen fibers, consistent with neurofibroma (Figure 6).

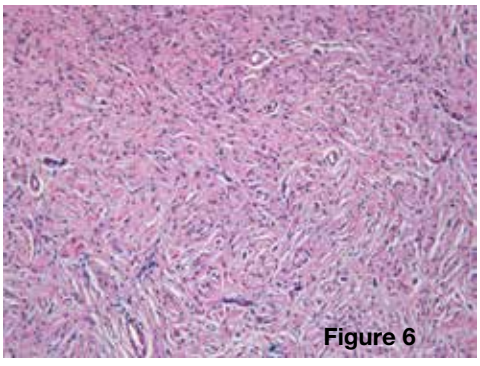

Figure 6

Because of lack of regular follow-up with any physicians, a complete blood count and comprehensive metabolic panel were done and were within normal limits. An MRI of the brain was only significant for post-surgical change, without any evidence of intracranial masses. CT of the abdomen without contrast was negative for significant changes.

Discussion

Classic neurofibromatosis is the most common subtype of the NF spectrum, representing at least 90% of the cases of neurofibromatosis and affecting approximately 1 in 3,500 people.[3] Inherited autosomal-dominantly, the gene is located on chromosome 17 and is regarded as a tumor-suppressor gene.[6] However, half the patients diagnosed with NF1 are the first persons in their families to be afflicted, reflecting an approximate 50% sporadic mutation rate.[7]

Though the vast majority of NF patients demonstrate features of classic NF, forming the basis of its diagnostic criteria (Table 1), much diversity exists in the neurofibromatosis syndromes. In recognition of the heterogeneity of this disease, it was classified into eight different categories based on clinical features by Riccardi in 1982 (Table 2).[8] Riccardi Type V of the VIII, segmental neurofibromatosis, is a rare variant that represents the genetic mosaic phenomenon and clinically presents more subtly than the classic type. In fact, the majority of patients, such as the two presented in this report, are asymptomatic and without positive family histories, presenting for dermatologic consultation well into their

Table 1. Diagnostic Criteria for Neurofibromatosis 1

Diagnosis requires two or more of the following:

Cutaneous Findings:
- ³6 café-au-lait macules >5 mm in greatest diameter in prepubertal persons and >15 mm in greatest diameter in postpubertal persons
- Axillary/inguinal freckling (Crowe's sign)
- 2 or more neurofibromas of any type or at least 1 plexiform neurofibroma

Skeletal Findings:
- Osseous lesion such as kyphoscoliosis, sphenoid dysplasia, or thinning of the long-bone cortex with our without pseudoarthrosis
- 2 or more Lisch nodules
- Optic glioma

Other:
- A first-degree relative (parent, sibling, or offspring) with neurofibromatosis 1 by the above criteria
- Discovered mutation of NF1 gene

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Table 2. Riccardi Classification of the Neurofibromatoses

Category	Description	Phenotypic Features
NF-I	Von Recklinghausen	Heritable, diffuse café -au-lait spots, diffuse neurofibromas, Lisch nodules, CNS-derived neural-crest tumors
NF-II	Acoustic	Heritable, few and large diffuse café-au-lait spots, few neurofibromas, BL acoustic neuromas, no Lisch nodules
NF-III	Mixed: Mixture of primary features of NF1 and NF2	Heritable, diffuse café-au-lait spots, variable to few neurofibromas, multiple CNS brain and spinal-cord tumors (hallmark)
NF-IV	Variant	Diffuse café-au-lait spots and neuromas
NF-V	Segmental	Café-au-lait spots and neurofibromas with distribution limited to a given region of the body
NF-VI	Café-au-lait spots	Diffuse café-au-lait spots, no neural fibromas, no other neural-crest tumors
NF-VII	Late onset	Diffuse neurofibromas (cutaneous or deeper) in the 3rd decade of life or later
NF-VIII	Not otherwise specified	All other forms of NF that do not fit into the above categories

Table 3. Subclassification of Segmental Neurofibromatosis (Roth et al.)

Subcategory	Description	Phenotypic features
i	True segmental	Unilateral, localized without family history of neurofibromatosis
ii	Localized with deep involvement	Underlying deep systemic involvement
iii	Hereditary	Localized with genetic transmission of neurofibromatosis
iv	Bilateral	Bilateral cutaneous manifestations

adulthood for cosmetic concerns.

Historical Classification and Epidemiology

Segmental neurofibromatosis is an uncommon variant of NF1 and is characterized by disease limitation to one or more body segments (localized) as compared to involving the entire phenotype (generalized).[9] This particular disorder was first described in 1931 by Gammel, but was termed sectorial neurofibromatosis by Crow et al. in 1956.[10,11] Then in 1987, Roth et al. took Riccardi's Type V NF classification and further subdivided segmental NF into four subtypes (Table 3). However, by the end of the twentieth century, the cause of segmental neurofibromatosis had finally been elucidated and was found to be a mutation on NF1 gene.[5] As a result, this disease is now widely regarded as segmental neurofibromatosis type 1. Unlike classic NF1 and NF2, there is much ambiguity surrounding the diagnosis of segmental neurofibromatosis, as there is no definitive clinical criterion to diagnose the disorder. Approximately 150 cases of segmental neurofibromatosis have been described worldwide in the literature.[12] The estimated frequency worldwide is 0.0018%, which is 10 times more infrequent than the other types of neurofibromatosis.[13]

Clinical Presentation

Initially, most patients arrive in the office when they notice an unusual or disfiguring appearance to their skin. However, this condition is often underdiagnosed due to the absence of other symptoms of the other neurofibromatoses. The most common lesion is the cutaneous neurofibroma, which is present in 75% of patients, with café-au-lait macules appearing 40% of the time.[8] These lesions usually involve one side of the body and tend to affect the cervical, thoracic, lumbar and sacral regions.[7] It is important to note, however, there have been case reports of bilateral segmental neurofibromas, both in symmetric or asymmetric distribution. Adults tend to present with neurofibromas, while children present with pigmentary changes that follow similar patterns of presentation as classical NF1.[7] In most cases with pigmentary involvement, the borders of pigmentation follow the lines of Blaschko. The most common pigmented lesion is the café-au-lait macule, with the second most common being axillary freckling.[7] If the sole lesion is a cutaneous neurofibroma, the lesions are isolated to one dermatome or involve a major peripheral nerve or nerve plexus. They are usually discrete nodules that are asymptomatic with a skin-color to violaceous hue, ranging in size from 0.1 cm to several centimeters.[7] Puberty and pregnancy are the most common times associated with increased growth, and at least 25% of patients with neurofibromas experience significant pruritis.[3,14]

Genetics and Clinical Implications

The wide variety of presentations of segmental neurofibromatosis is in part secondary to the genetics behind the disease. The NF1 genes have one of the highest mutation rates in the human genome, and nearly 50% of all cases of NF1 represent new mutations.[6] As such, segmental neurofibromatosis occurs because of a somatic mutation of the NF1 gene and represents a mosaicism where there is the coexistence of both normal and mutant cell populations. The exact phenotype of the patient often varies between patients due to the timing of the mutation (early vs. late embryonic development) and the source of the tissue harboring the affected mutation.[7] The majority of cases are thought to represent a postzygotic somatic mutation of the NF1 gene after laterality has been established at around day 14 of embryonic development.[15] Thus the mutation would only affect the progeny of the mutant cell, limiting the phenotypic effect to a single, unilateral dermatome.[7] Conversely, if the mutation occurred before tissue differentiation, the clinical phenotype would be consistent with a generalized neurofibromatosis.

The majority of patients with segmental neurofibromatosis have no affected relatives with the disorder. Still, there are reports of parents with segmental neurofibromatosis having offspring with full-blown NF1.[7] This is likely due to mosaicism in the germ line cells and not the somatic cells. The chance that a parent who is mosaic for NF1 will have offspring with generalized NF1 is much lower than the expected 50% incidence for the autosomal-dominant NF type 1. The risk for a sibling of an affected child from a parent who has mosaic expression of NF1 is likely an empiric recurrence risk of below 3%.[16] The exact risk of having a child with generalized NF1 is not definable, yet animal-based studies with chimeric mice have found that the risk may be proportional to the percentage of body surface area involved.[7] When evaluating a patient for genetic counseling, it may be more useful to evaluate a male since 90 percent of the sporadic NF1 mutations arise in paternally inherited alleles.[6]

Suspected patients should be counseled on the clinical differences and key associations between classic generalized NF1 and the more subtle entity. However, it is significant to remember that segmental NF1 should be approached as a localized phenotype of NF1, not a separate form of neurofibromatosis, so that crucial screening is not overlooked.[6] The presence of optic gliomas and Lisch nodules has been reported, but it is important to note that these lesions were not always ipsilateral to the side of the cutaneous manifestation.[7] Although a recommendation for ophthalmologic screening in all cases of segmental NF is undetermined, a conservative approach of thorough ophthalmologic screening is supported by many authors.[17,18]

The lifetime risk of developing a malignancy with classical NF1 is 5% to 15%, which is about 2.5 times the risk seen in the general population.[19] The incidence of cancer in patients with segmental neurofibromatosis has been approximated at 5.3%.[20] The most common malignancy with segmental neurofibromatosis is malignant peripheral nerve sheath tumor. Progression from a neurofibroma to a malignant peripheral-nerve-sheath tumor ranges from 2% to5%, compared with 0.0001% in the general population.[21] Thus, a patient with segmental NF is 4,000 times more likely to have malignant progression of the neurofibroma. Patients should be closely monitored for rapid growth of the tumor, pain and neurological deficits that may demonstrate the rise of a malignant peripheral nerve sheath tumor.

The second most common malignancy that arose was malignant melanoma, which, like nerve sheath tumors, is of neural crest cell origin.[20] With NF1, the mechanism behind the melanoma is believed to be associated with an increased number of melanocytes in the café-au-lait spots as well as in normal skin and associated inactivation of the NF1 gene in the melanoma cell lines.[22] When comparing melanomas in patients with NF1 to the general population, these patients were more likely to be female, have a lower age at diagnosis and have a higher Breslow thickness.[23] Other reported malignancies were breast, colon, gastric, lung and lymphoma.

Conclusion

A patient may present with very subtle lesions fitting the category of segmental NF. In the examination of patients with potential segmental NF, at least a thorough family history and full clinical and ophthalmologic examination should be undertaken, with positive findings dictating more specific imaging and workup. Further consideration of pre-natal counseling, particularly in men, should be considered so that the risks are explained to potential parents. Over time, these patients may be at risk for more malignancies than the general population. More cutaneous or systemic associations could eventually result in re-classification of the disease and warrant closer screening besides age-appropriate screening in adults.

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Correspondence: Sarah Ferrer-Bruker, DO; Sarahferrerbruker@gmail.com.

Increased Frequency of Histologic Diagnosis of Syphilis in Older Individuals During the Last Five Years

Jamie Groh, DO,* Willmar D. Patino, MD**

*Dermatology Resident, PGY-V, West Palm Beach Hospital, Palm Beach Consortium for Graduate Medical Education, West Palm Beach, FL
**Dermatopathologist, Dermpath Diagnostics South Florida., Pompano Beach, FL

Abstract

The incidence of Syphilis has been incrementally increasing in the United States since the year 2000. It is important to identify high-risk population groups in order to provide earlier diagnosis and preventive education. We sought to assess the incidence of syphilis in the elderly population (over the age of 50) in the last five years compared to the five years prior. The keywords syphilis, lues, and treponema were used in the WinsQUERY feature of WinSURGE to extract all the cases of syphilis diagnosed at Dermpath Diagnostics in Pompano Beach, Florida, during the last 10 years (January 1, 2003 to December 31, 2012). Pathology review was limited to reports only. The presence of spirochetes were detected by either Steiner silver stain or immunohistochemical stain for Treponema pallidum. Immunohistochemical staining is more sensitive and specific.

From 2008 to 2012, there was a 31.6% increase in the incidence of syphilis in patients over the age of 50 diagnosed in our laboratory compared to 2003 to 2007. Given the variability in clinical and histologic presentation, clinicians as well as pathologists should consider syphilis in their differential diagnosis when treating older patients.

Introduction

Syphilis is a multistage, sexually transmitted, chronic infection caused by Treponema pallidum. It is found worldwide and has afflicted humanity since at least the fifteenth century. Although it was major cause of morbidity and mortality in the early twentieth century, the introduction of penicillin and public health programs so greatly reduced the number of cases in most first-world countries by the midcentury that most physicians are now unfamiliar with its signs and symptoms. In the late 1980s, there was an increase in the infection rate in the rural south and urban regions of the United States; but after that, the number of syphilis cases declined, and in 2000 it fell to its lowest point since reporting began in 1941.[1] Since 2000, the number of reported cases of syphilis has risen, with an estimated 55,400 new infections diagnosed per year in the United States.[2] Centers for Disease Control (CDC) data show an increased incidence of primary and secondary syphilis in the general population, from 3.8/100,000 in 2007 to 4.5/100,000 in 2011.[1] In line with the CDC findings, in our dermatopathology laboratory we have observed an increased frequency in the histologic diagnosis of syphilis during the last decade, particularly in men over the age of 50, which is a population often not targeted for preventative education or screening.

Table 1. Demographic Information of Patients Diagnosed with Syphilis Between 2003 and 2012

Number of patients	65
Males	60
Females	5
Patients >50 years old	18 (27.7%)
Biopsy location	
Head and Neck	4
Trunk	34
Extremities	20
Palms and Soles	5
Genitals	12
Total number of biopsies	75
Average number of biopsies per patient	1.15
Biopsies submitted with diagnosis of syphilis	24 (32%)
Biopsies submitted with diagnosis other than syphilis	51
Diagnosis confirmed by silver stain	4
Diagnosis confirmed by immunohistochemical stain	71
Diagnosis consistent with primary syphilis	12

Methods

Data Source

The keywords syphilis, lues, and treponema were used in the WinQUERY search feature of WinSURGE, our Windows-based anatomic pathology system. From this search we were able to extract all the cases of syphilis diagnosed in our laboratory during the last 10 years (January 1, 2003 to December 31, 2012). We selected cases of syphilis in which the diagnosis was confirmed by the histologic findings in conjunction with the presence of spirochetes detected by a special stain (Steiner) and/or immunohistochemical stain for Treponema pallidum. Demographic information, anatomic location of biopsies, clinical history submitted with the biopsy, and histologic findings were collected in these cases and used for statistical analysis (Table 1).

Analysis

To accurately assess the frequency of syphilis cases and eliminate the variable factor of volume of biopsies seen in the laboratory each year, we "normalized" the rate of diagnosis of syphilis for every 100,000 biopsies: (Number of biopsies diagnostic of syphilis in a year/number of biopsies seen in our laboratory that year) x 100,000. We then compared the yearly average rates of syphilis as well as average rates of syphilis in 2003 to 2007 as compared to 2008 to 2012 both in the entire population and in those over the age of 50.

Results

Seventy-five biopsy specimens from 65 different patients were found to be diagnostic of syphilis in our dermatopathology laboratory between January 1, 2003 and December 31, 2012. Out of these biopsies, only 32% came with clinical history of syphilis. Of these 65 patients, 60 (92.3%) were men. Ages ranged from 19 to 73. Out of these, 18 (27.7%) were older than 50 (17 males and one female). Furthermore, seven (10.7%) patients (all males) were older than 60 (Table 1).

The majority of biopsies were from the trunk and extremities. The diagnosis of syphilis was confirmed on histologic grounds plus identification of spirochetes using Steiner (four biopsies) and/

Table 2. Number and Rate of Biopsies Diagnostic of Syphilis Between 2003 and 2012

Year	Number of biopsies diagnostic of syphilis	Rate of biopsies diagnostic of syphilis (x100,000)
2003	0	0
2004	3	1.27
2005	1	0.44
2006	0	0
2007	4	1.08
2008	6	1.46
2009	11	2.53
2010	25	6.56
2011	17	4.84
2012	8	2.14
	Total: 75	Average: 2.032

or immunohistochemical stain for Treponema pallidum (71 biopsies). The diagnosis of primary syphilis was made on 12 biopsies (Table 1).

The number and rate of biopsies diagnostic for syphilis increased significantly since 2003, which was seen both in our laboratory and in the statistical data presented by the CDC (Table 2, Figures 1 and 2). Furthermore, when comparing the rates between the periods 2003 to 2007 and 2008 to 2012, we observed a significant increase in the cases of syphilis. The average rate increased from 0.56/100,000 biopsies (eight patients) to 3.51/100,000 biopsies (57 patients) (Figure 3). This corresponds to ~630% increase in the average rate of biopsies diagnostic for syphilis in the last five years.

This trend was also true for older individuals. During the period of 2003 to 2007, we did not identify any cases of syphilis in patients older than 50. However, during the following five years we identified 18 cases of syphilis (21 biopsies) in individuals older than 50 (Figure 3). That corresponds to 31.6% of all the patients diagnosed with syphilis during that five-year period. Furthermore, those patients older than 60 represented 12.3% of the cases. Therefore, the average rate of biopsies diagnostic for syphilis in individuals older than 50 went from zero between 2003 to 2007 to 1.08/100,000 biopsies diagnosed in our laboratory between 2008 and 2012.

Discussion

Syphilis is a sexually acquired, chronic infection caused by Treponema pallidum and is characterized by a variety of clinical manifestations as it progresses through active and latent stages, earning it the title of "the great mimicker." There is great variability in the presentation of syphilis both clinically and histologically, making it difficult to diagnose. In our dermatopathology laboratory, only 32% of the biopsies diagnosed as syphilis came with a clinical history or suspicion of the disease. The diagnosis of syphilis includes correlation of clinical, serological and histologic findings.

The clinical presentation of syphilis is divided into four main stages: primary, secondary, latent (early and late) and tertiary.

1. Primary syphilis is a local infection of T. pallidum of the subcutaneous tissue. The initial ulcerative lesion, the chancre, occurs approximately 10 days to 90 days after infection at the site of inoculation and is characterized by a non-painful skin lesion in which the organism can be identified. Lesions typically heal within a few weeks without treatment. These lesions can easily be missed or incorrectly attributed to other common causes of genital or oral ulcers such as herpes, Hemophilus ducreyi, trauma, fixed-drug eruption or Behcet's disease.[1-4]

2. Secondary syphilis results from hematogenous dissemination and multiplication of the organism in different tissues, either simultaneously or within six months after healing of the primary lesions, and has numerous skin and systemic presentations. Skin manifestations can include a generalized eruption of brown-red macules and papules involving palms and soles, alopecia, condyloma lata and shallow painless mouth ulcer. After three to 12 weeks, most skin lesions typically spontaneously disappear. The cutaneous findings of secondary syphilis can be confused with pityriasis rosea, guttate psoriasis, viral exanthems, lichen planus, pityriasis lichenoides chronica, primary HIV infection, drug eruption, nummular eczema or folliculitis.[1-5]

3. Latent syphilis is a period in which patients infected with T. pallidum have no symptoms but have positive serologic testing. This stage can last for many years. Approximately 70% of untreated individuals will stay in the latent stage for the rest of their lives. Latent syphilis is subdivided into early (less than one year) and late (more than one year). Patients may relapse and develop signs of secondary syphilis, never have another recurrence, or may develop tertiary syphilis.[1-3]

4. Tertiary or late syphilis is characterized by the presence of a small number of organisms and high cellular immune reactivity against the organism. Damage is related to a delayed-type hypersensitivity response, which produces local inflammation and gummas in affected tissues. The most common manifestations of late syphilis include:

Figure 1

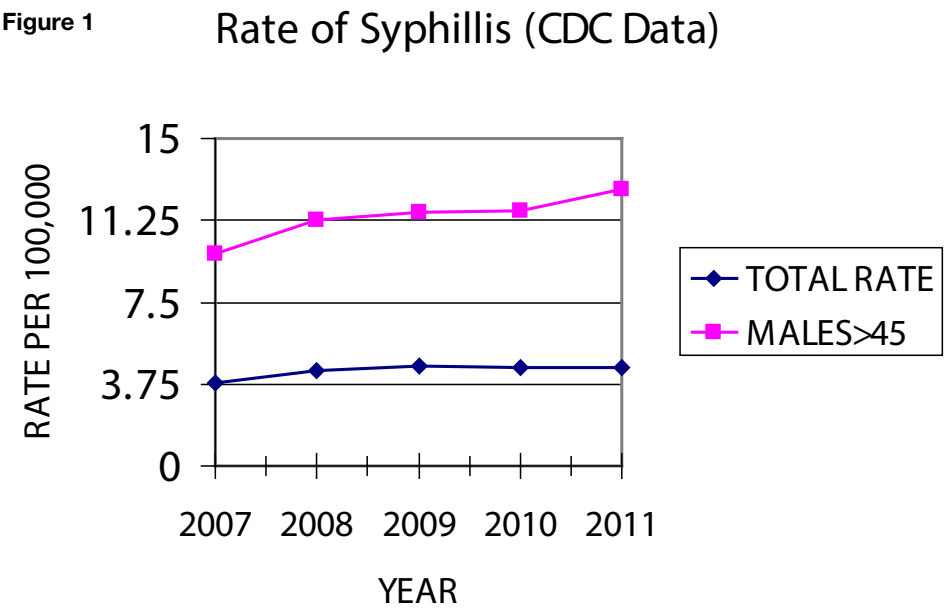
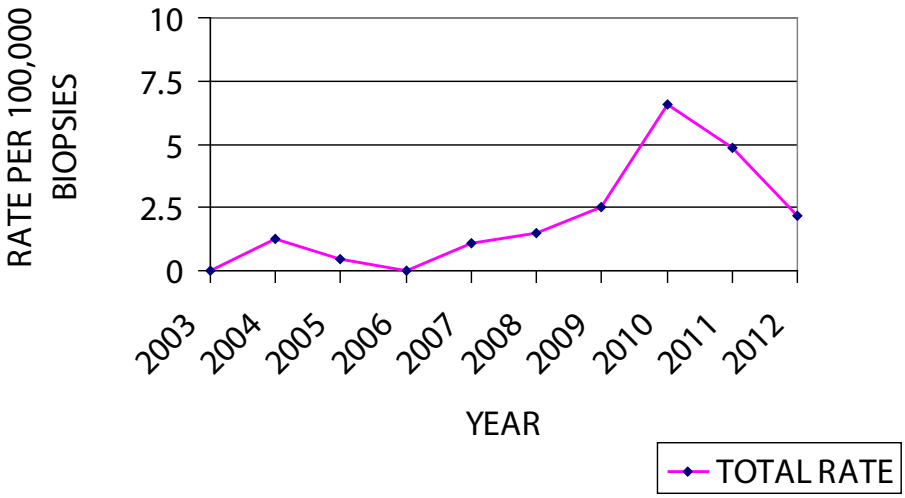


Figure 2 Total Rate of Biopsies Diagnositc of Syphilis



Central nervous system involvement or neurosyphilis (acute syphilitic meningitis, tabes dorsalis, optic nerve atrophy, Argyll Robertson pupils and cerebrovascular syphilis secondary to syphilitic endarteritis)

Cardiovascular syphilis (aortitis)
Gummatous syphilis (granulomatous, nodular lesions that can affect a variety of organs, most commonly skin and bone; often mistaken for lupus vulgaris, chromoblastomycosis, dimorphic fungal infections, leishmaniasis, lupus erythematosus, mycosis fungoides, sarcoidosis or tumors)[1,2]

The diagnosis of syphilis is most commonly made by serologic testing, as T. pallidum cannot be cultured in the laboratory; therefore, syphilis must be identified in clinical specimen or by serology. The spirochetes are usually identifiable by dark-field microscopic exam in the primary and secondary lesions. Serologic tests are helpful in the secondary stages and include treponemal and non-treponemal antibody tests. Non-treponemal tests, including venereal diseases reference laboratory tests (VDRL) and rapid plasma reagin test (RPR), identify antibodies to cardiolipin and are only positive with active disease. The treponemal tests include T. pallidum haemabsorption test (TPHA), micro-haemagglutination assay for antibodies to T. pallidum (MHA-TP) and fluorescent treponemal antibody absorption assay (FTA-ABS). These tests detect antibodies to the surface proteins of T. pallidum and remain positive after treatment. The standard algorithm for diagnosis starts with a screening non-treponemal test, such as an RPR. If the test is positive, then a confirmatory treponemal test such as FTA-ABS is done, as false-positive RPR can occur due to lupus erythematosus, lymphoma, antiphospholipid syndrome, cirrhosis, vaccinations, drug abuse and HIV. If both are positive, then the diagnosis of syphilis is confirmed.[1-5]

While not the gold standard for diagnosis, T. pallidum spirochetes can also be identified on histopathology. Spirochetes can be seen with silver stains or immunohistochemical staining more in primary than secondary or tertiary lesions. The typical presentation of syphilis histologically depends on the stage and type of lesion biopsied. In a chancre of primary syphilis, there is ulceration of the epidermis, psoriasiform epidermal hyperplasia, typically with elongated rete and a diffuse perivascular and interstitial dermal infiltrate of plasma cells, lymphocytes and histiocytes. Spirochetes are usually identified within and around blood vessels and at the dermal-epidermal junction.[5-8]

In secondary syphilis, the epidermis may be normal, psoriasiform, necrotic or ulcerated. Pustules may also be found in the epidermis. Dermal infiltrates of plasma cells, lymphocytes and histiocytes can be perivascular, lichenoid, nodular or diffuse (Figures 4 and 5). Spirochetes can only be identified in one third of cases, usually in the epidermis, when using silver stain, but can be identified in most cases on immunohistochemical staining (Figure 6). Tertiary syphilis presents as a caseating or non-caseating granuloma, and spirochetes are usually not identified.[6-9]

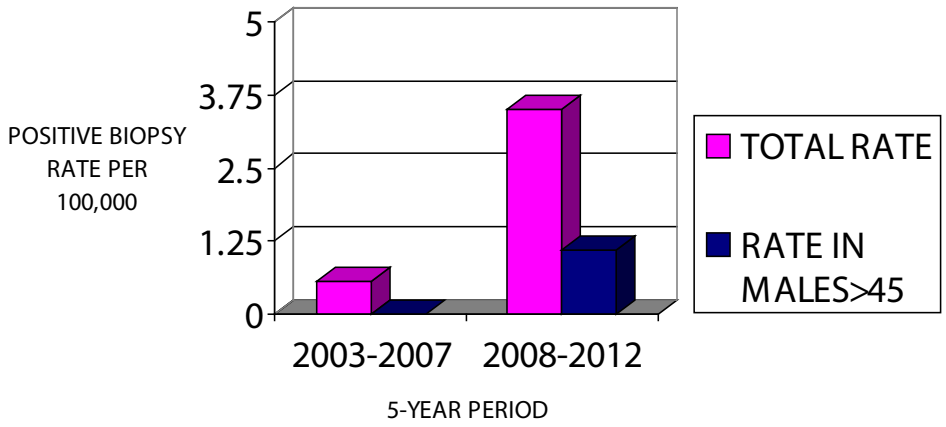
In the past decade, there has been increasing incidence of syphilis. We have observed a similar increase in frequency of histologic diagnosis of syphilis in our laboratory in recent years. We also found a significant increase in diagnosis in patients over the age of 50.

The elderly population is often not targeted for education on sexually transmitted diseases (STDs) because it is assumed they are no longer participating in sexual activity. Data from the University of Chicago's National Social Life, Health and Aging Project (NSHAP), presented in the August 23, 2007 issue of the New England Journal of Medicine, showed that many men and women remain sexually active well into their 70s and 80s. The prevalence of sexual activity declined with age: 73% of the people who were aged 57 to 64 years reported that they had sex with at least one partner in the previous year, but only 53% of those who were aged 65 to 74 years and 26% of those who were aged 75 to 85 years reported being sexually active.[10] In this population, there are numerous widows and widowers who are finding new sexual partners for the first time in many years and are not educated on the prevalence of STDs. Data from the CDC shows an increased incidence of all STDs in the elderly population, not just syphilis.[1] The rise in STDs can be explained by numerous factors, including a false sense of security, particularly in postmenopausal women with no risk of pregnancy, and a subsequent false perception that there is no need for other protection. Also, the lack of education from primary care givers or public health care groups contributes to this growing epidemic. In the NSHAP survey, it was found that only 22% of women and 38% of men had discussed sex with a doctor since age 50.[10]

Another factor possibly adding to increased incidence of STDs in the elderly population during the last decade(s) is the readily available medications

Comparison Rate of Syphilis Between 2003-2007 and 2008-2012

Figure 3



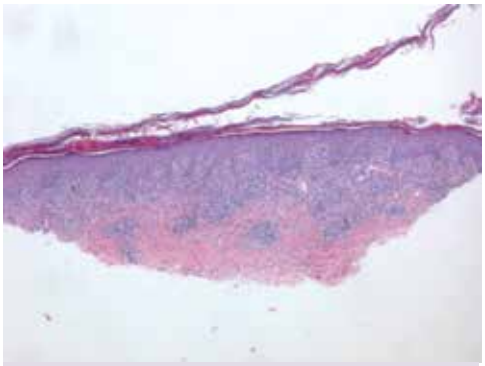


Figure 4. Shave biopsy from the left foot of a 60-year-old male. Biopsy came in with differential diagnosis of psoriasis vs. allergic drug eruption. At 5x magnification, one can see epidermal hyperplasia with an underlying lichenoid lymphocytic infiltrate consistent with secondary syphilis.

for erectile dysfunction. In the NSHAP study, one out of seven men (14%) admitted to using erectile dysfunction medications.[10] Some articles report an association between use of erectile dysfunction medications and increased STDs. However, an article from the Annals of Internal Medicine showed that men who used erectile dysfunction (ED) medications had higher rates of STDs in the year before and the year after starting the medication.[11] The observed association between ED drug use and STDs may have more to do with the types of patients using ED drugs rather than a direct effect of ED drug availability on STD rates.[11,12] Counseling about safe sexual practices and screening for STDs should accompany the prescription of all ED drugs.

Limitations

This was a retrospective review of pathology reports; we were unable to review the histopathologic slides.

Our results could be due in part to the availability of a more sensitive and specific method to diagnose syphilis (T. pallidum immunostain instead of Steiner special stain). Immunostaining is more sensitive and specific than silver stain for detecting T. pallidum in biopsies of secondary syphilis.[9] Silver stains shows spirochetes in one third of secondary syphilis cases, typically in the epidermis, while immunohistochemical staining is positive in all cases.[7] In our laboratory, we started using the immunostaining in 2007, which could account for an increase in diagnosis, although there were still no cases diagnosed in patients over 50 years old until 2008.

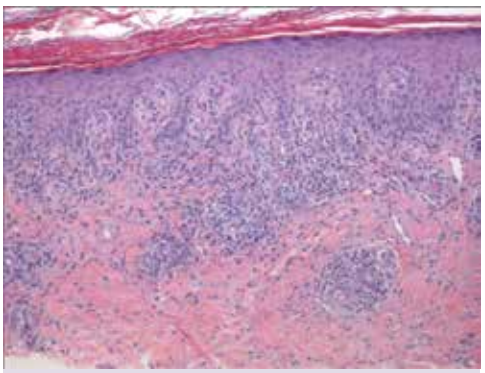


Figure 5. Higher magnification (20x) reveals that the infiltrate is composed of lymphocytes and some scattered plasma cells.

Finally, the biopsies we reviewed were primarily from patients in Florida. There may be population bias that relates to the increased incidence of syphilis seen in the elderly population. According to the 2013 census, Florida's percentage of persons over the age of 65 was 18.7%, compared to the United States average of 14.1%.[13]

Conclusion

We identified a significantly increased rate of biopsies diagnostic of syphilis, particularly in older individuals, in the last five years. The diagnosis of syphilis has significant implications for patients and sexual contacts. The CDC recommends routine screening for syphilis in high-risk populations, including those with multiple sex partners and those practicing unprotected intercourse. The rationale for screening for syphilis in asymptomatic patients is related to the natural history of the disease and to issues of public health. Unfortunately, the elderly population is often left out of the preventative education and screening, as they are incorrectly assumed to no longer be at risk. In the early stages, syphilis is easily treated, and early treatment prevents complications associated with the late stages of disease. Therefore, it is critical to take a thorough sexual history on all patients, regardless of age, as well as recognize and treat this disease as early as possible. Given the variability in clinical and histologic presentation, clinicians as well as pathologists should consider it in the differential diagnosis regardless of the age of the patient.

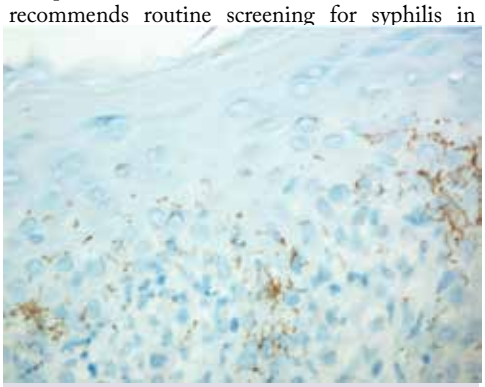


Figure 6. Immunohistochemical stain for Treponema pallidum shows numerous spirochetes staining brown along the dermal-epidermal junction.

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