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EDITORIAL

Superficial Basal Cell Carcinoma of the Skin Is a Cutaneous Basal Cell Carcinoma *In Situ*

Philip R. Cohen, MD

As a medical student (1979–1983), dermatology resident (1986–1989), dermatopathology fellow (1990–1992), and a dermatopathologist (since 1992), I have learned and believed that a cutaneous basal cell carcinoma *in situ* was not a recognized variant of basal cell carcinoma. Indeed, dogma is accepted as truth until it is no longer valid. After more than 40 years in medicine, I realized that—similar to squamous cell carcinoma *in situ* and melanoma *in situ*—cutaneous basal cell carcinoma *in situ* does exist but has been misidentified as a superficial basal cell carcinoma.

SUBTYPES OF BASAL CELL CARCINOMA

Basal cell carcinoma is an invasive skin cancer comprising nests or islands of basaloid cells; in the center of the nests, the tumor cells have a haphazard arrangement and at the periphery of the islands, there is palisading of tumor cells. Superficial basal cell carcinoma, which only accounts for 10% to 15% of basal cell carcinomas, is usually confined to the papillary dermis and comprises small nests of basaloid tumor cells attached to the underside of the epidermis without noncontiguous invasion into the dermis. In contrast, nodular basal cell carcinoma, which comprises nearly 70% of basal cell carcinomas, consists of islands of tumor cells in the dermis—at least some of which are not attached to the overlying epidermis—whose central cells have a haphazard arrangement.[1]

ORIGIN OF BASAL CELL CARCINOMA

The origin or the differentiation, or both of a basal cell carcinoma may influence its pathologic subtype and development into an invasive neoplasm. Basal cell carcinoma most frequently has been attributed to originating from embryonic follicular germinative cells;[2–4] however, investigators have also demonstrated that some basal cell carcinomas arise from the basal layer of the interfollicular epidermis.[5]

DIFFERENTIATION OF BASAL CELL CARCINOMA

It has been established that adnexal differentiation is an extremely common property of basal cell carcinoma. Although follicular germinative cells are not normally present in the epidermis, mature cutaneous epithelium demonstrates contiguity of the epidermis with hair follicles. Indeed, the superficial basal cell carcinoma recapitulates the embryonic development of follicular germ cells; specifically, it represents a faulty attempt at differentiating follicular germinative cells.[2–4] Consequently, it is expected that a superficial basal cell carcinoma may emanate from follicular epithelium; however, if the tumor cells remain contiguous with the follicle—without any noncontiguous invasion into the adjacent dermis—the neoplasm would be classified appropriately as an *in situ* carcinoma.

DEFINITION OF "*IN SITU*"

The translation of "*in situ*" from Latin means "in its (original) place or position."[6] According to a medical resource, "an *in situ* tumor is one that is confined to its site of origin and has not invaded neighboring tissue or gone elsewhere in the body."[7] Similarly, the National Cancer Institute provides a denotative histopathologic definition of carcinoma *in situ as* "a condition in which abnormal cells that look similar to cancer cells under a microscope are found only in the place where they first formed and have not spread to nearby tissue."[8] Accordingly, the connotative meaning of basal cell carcinoma *in situ* of the skin is a neoplasm—whose "site of origin" where it is "first formed" is the epidermis—consisting of tumor cells that are not only confined within the epidermis but also do not exhibit noncontiguous invasion into the "nearby" or "neighboring" tissue of the dermis.

DEFINITION OF CUTANEOUS CARCINOMA *IN SITU*

The designation of an *in situ* carcinoma—and particularly a cutaneous carcinoma *in situ*—is not predicated by the thickness of

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the epithelium in which it originates. For instance, a squamous cell carcinoma *in situ* of the skin can present itself in a thickened epidermis that expands beyond the papillary dermis and into the reticular dermis. Similarly, intraepidermal proliferation of the tumor cells of a cutaneous basal cell carcinoma *in situ* can result in a markedly thickened epidermis with contiguous extension of the *in situ* neoplasm into the underlying papillary dermis. At the same time, the neoplasm remains *in situ* provided that individual tumor cells, and nests of cancer cells are not present as isolated cancer cells and/or tumor islands in the dermis.

DEFINITION OF INVASIVE BASAL CELL CARCINOMA

In contrast, skin cancer invasion could be described as the presence of noncontiguous nests of tumor cells or individual cancer cells in the dermis. Indeed, it could be reasonable to define an invasive basal cell carcinoma as a tumor in which the neoplastic cells have breached the epidermis with penetration of the epidermal basement membrane; thereby, the neoplasm demonstrates individual cancer cells or islands of tumor cells, or both in the dermis without attachment to the overlying epidermis. The future studies evaluating the integrity of the basement membrane in superficial basal cell carcinoma and other pathologic variants of basal cell carcinoma could be useful to support the concept that a superficial basal cell carcinoma is a basal cell carcinoma *in situ*.

BASAL CELL CARCINOMA WITH MIXED HISTOLOGY

Basal cell carcinoma with mixed histology is a pathologic variant of basal cell carcinoma in which two or more pathologic subtypes of the cancer are present.[1,9] Investigators have observed neoplasms containing superficial basal cell carcinoma restricted to the epidermis and other basal cell carcinoma subtypes (such as infiltrating, nodular, micronodular, morpheaform, and/or sclerosing) in the deeper papillary dermis, the reticular dermis, or both.[1,9,10] Nevertheless, based on the absence of tumor cell invasion of the superficial basal cell carcinoma subtype (which emanates from the undersurface of the epidermis and projects—remarkably similar to how a follicular germ develops in the skin of an embryo—in an arciform shape into the papillary dermis), it is more appropriate to define the unique pathologic presentation of basal cell carcinoma with mixed histology to concurrently contain both *in situ* carcinoma restricted to the epidermis and invasive cancer occupying the dermis.

CUTANEOUS BASAL CELL CARCINOMA *IN SITU*

After I had my epiphany, I published a case series of cutaneous basal cell carcinoma *in situ*, in which the clinical and pathologic characteristics of this *in situ* variant of basal cell carcinoma were described.[11] The neoplasm typically appears on the trunk or extremities as an erythematous plaque (Figure 1); microscopically, the basaloid tumor cells either replace the lower layers of the epidermis (with or without contiguous extension into the papillary dermis) and/or partially fill (with occasional expansion of) the epidermis (Figure 2). Indeed, the nonaggressive pathologic features of this tumor correlate with the clinical observation that multiple therapeutic modalities have been used successfully to treat the neoplasm.

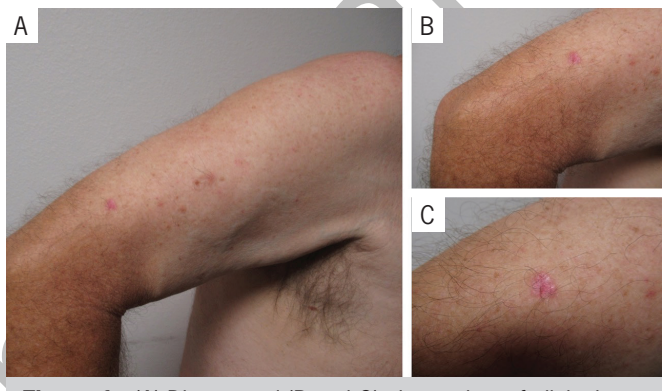

Figure 1. (A) Distant and (B and C) closer view of clinical presentation of basal cell carcinoma *in situ* as an asymptomatic red scaly plaque on the mid upper right arm of a 62-year-old man.

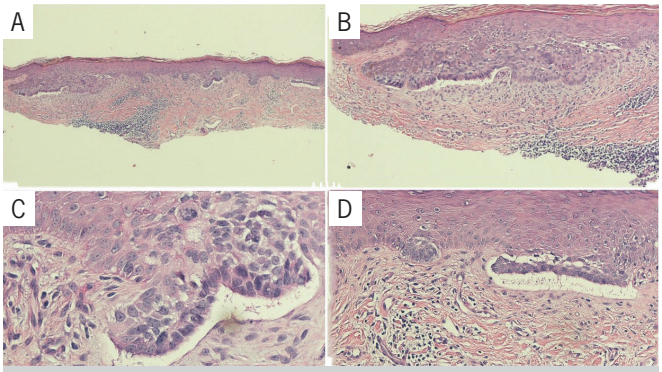

Figure 2. Pathology presentation of basal cell carcinoma *in situ*. (A) Lower and (B–D) higher magnification view of a basal cell carcinoma *in situ* on the mid upper right arm of a 62-year-old man shows not only aggregates of basaloid tumor cells that extend from the overlying epidermis (without noncontiguous invasion) into the underlying dermis (A–C) but also a linear arrangement of atypical cells along the basal layer of the epidermis (A and D). There is also a retraction of dermal stroma from the cancer cells located at the periphery of the basaloid tumor cell aggregates and along the epidermal basal layer (A–D) (hematoxylin and eosin [H&E] stain, magnification: (A) ×4; (B) ×10; (C) ×40; and (D) ×20).

CONCLUSIONS

In summary, the absence of noncontiguous tumor invasion of a cutaneous neoplasm from the overlying epidermis into the underlying dermis defines an *in situ* carcinoma of the skin. The time has arrived for clinicians and pathologists to embrace the existence of cutaneous basal cell carcinoma *in situ*. In conclusion, superficial basal cell carcinoma of the skin is a cutaneous basal cell carcinoma *in situ*.

CONFLICT OF INTEREST

Dr. Cohen is a consultant for ParaPRO (Indiana, USA); however, there was no conflict of interest about this manuscript. Dr. Cohen had no source of funding.

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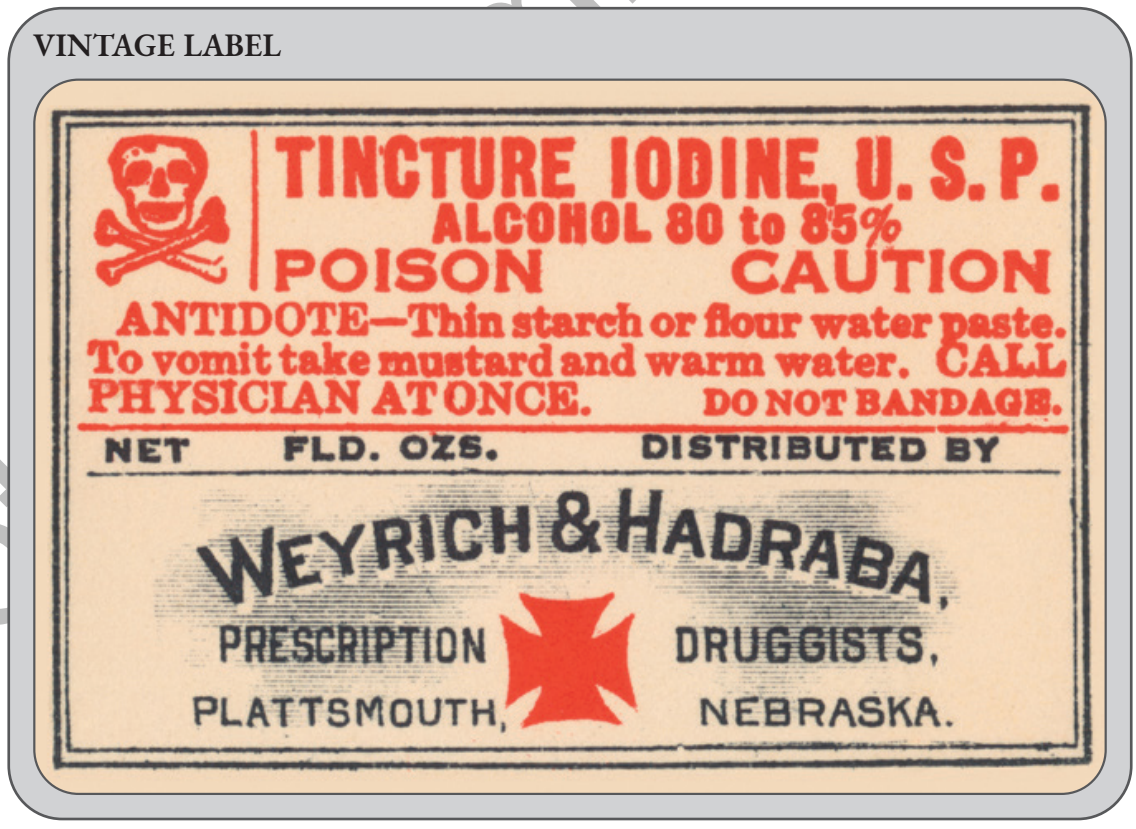

COMMENTARY

Best Practices in Hiring Ancillary Staff in Dermatology Clinics

Anika Mazumder, BS; Sino Mehrmal, DO; Dee Anna Glaser, MD

ABSTRACT

Increased turnover and burnout of healthcare workers because of the COVID-19 pandemic made hiring ancillary staff in dermatology clinics a challenging task. As the dermatologic requirements of an aging population grow, demand for ancillary staff has also increased. We reviewed evidence-based strategies, best practices, and specific examples pertinent to dermatology to improve recruitment, hiring, and retention of nonphysician staff in dermatology clinics. (*SKINmed*. 2024;22:168–170)

Demographic shifts toward an elderly population with increased healthcare requirements have substantial implications for the dermatology workforce.[1] Almost half of dermatology patients are aged more than 60 years, and about 50% of individuals aged more than 65 years develop skin cancer.[1] We anticipate more job opportunities and the demand for increased ancillary staff in dermatology clinics in the future, although the "Great Resignation" of 2021 in addition to the COVID-19 pandemic made the hiring of nonphysician staff a challenging task. Around 18% of healthcare workers quit their jobs and 31% of retained employees have considered leaving the vocation.[2] Some chose to work from home or in different industries with similar or better salaries. With high patient volume and fast-paced clinics, dermatology staff are especially susceptible to burnout and high employee turnover. Given these challenges, we reviewed evidence-based strategies and best practices to improve the recruitment and retention of nonphysician staff in dermatology clinics.

RECRUITMENT

The first step of recruitment is to list available positions and relevant job descriptions on different recruitment platforms. These can include multi-industry websites, such as Indeed, Glassdoor, Monster, LinkedIn, and CareerBuilder as well as healthcare-specific websites, such as Health eCareers, JAMA Career Center, and MedicalJobs. Implementing a referral system from the present employees is also an efficient and effective mode to recruit suitable candidates.[3] The increasing inpatient demands during the COVID-19 pandemicresulted in greater turnover among hospital nurses, compared to ambulatory nurses because of increased burnout and inadequate staffing,[4] thus dermatology clinics with a close proximity to or affiliated to a hospital may benefit from recruitment of skilled inpatient nurses.

In addition to the duties and responsibilities of the position, postings should include competencies (e.g., skills, knowledge, and behavior) an employee must have to successfully perform the job.[5] Examples include computer, interpersonal, and accounting skills, knowledge of nursing or finance, and professionalism, collegiality, and multicultural sensitivity.[5] Important competencies specific to dermatology medical assistants (MAs) and nurses included skills to perform local anesthesia and drawing up injectable medication, setting up surgical trays, wound care (e.g., placing Unna boots, excision, and post-operative dressing changes), enrolling patients into risk evaluation and mitigation strategy portals (e.g., iPLEDGE for isotretinoin), call-backs for laboratory results, and a myriad of responsibilities important for MAs or nurses-only visits, including administering vaccines, suture removal, and post-operative wound checks. Other important skills include a basic knowledge of common dermatologic conditions and medications and the clinic's specific electronic medical record. Competencies that are applicable to all healthcare specialties include the ability to provide patient-centered and evidence-based care, identifying and applying quality improvement, work in interdisciplinary teams, and use of technology.[6]

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Competency-based job descriptions improve the accuracy of objectively assessing an applicant's suitability for a position and prevent assessment based on characteristics less relevant to the job.[5] It is important to include not only what an employer wants from an employee but also why an employee would want the job. Advertising the job's advantages, such as a competitive salary, benefits, access to learning opportunities, and autonomy of work experiences, can solicit applications from competitive applicants. The strengths of working in a dermatology clinic, such as caring for patients of all age groups, consistent hours, few emergencies, and a diversity of work experiences in medical, surgical, and cosmetic dermatology must be emphasized in the job description.

HIRING

Following recruitment, employers must appoint a selection panel and meet applicants to gauge their competence for the position. A selection panel ensures that several viewpoints are incorporated into the hiring process. The selection panel must include representatives from the groups the appointee will work with.[7] Like most other healthcare specialties, dermatology requires collaboration and interprofessional communication; hence eliciting help from the present staff can more accurately assess communication and teamwork skills.

Interviews must be structured using behavioral scenarios that allow applicants to highlight their problem-solving skills authentically. Instead of asking about strengths, weaknesses, or personality traits, interviewees must be questioned about fictitious or historically challenging experiences and their insights to the experiences.[5] Employers and the present employees can identify issues that the applicant has to face in their functioning, and ask the applicant how they would react and respond to the situation. Examples include asking the interviewee to describe a situation when they had to make a decision under pressure or how would they resolve a particular issue.[5] Applicants may also be asked about potential conflicts, such as how they they would respond to an argumentative patient, how they would assist if the clinic was running behind, or how they would manage conflict of a co-worker. The assumption of this behavioral-based interview model is that the past performance and experiences are a more accurate indicator of the future behavior.[5] Technical competencies, such as typing accuracy and medical calculations, must be assessed and verified as well. In addition to credentials and clinical skills, behavioral scenarios may also assess many important nonclinical attributes. These qualities include leadership, ability to work with others, communication, professionalism, and willingness to participate in quality improvement programs.[7]

Employers should also use the interview to describe clearly the job expectations and organizational policies. These include what specific tasks the job entails, required working hours, benefits, and policies about promotions.[3,8] In addition, interviewees should have the opportunity to express their career values and aspirations, which can further aid in determining their suitability for the position.[8] Some nurses can wish to have more direct patient-involvement, such as assisting with dermatologic procedures or history-taking. While this is often welcomed in community or private practice settings, such tasks are often performed by medical students or residents in academic centers. Good communication during the interview will prevent false expectations, and improve employee satisfaction and the future retension.[7]

RETENTION

When a successful hiring is completed, it becomes crucial to focus on employee retention. Healthcare occupations have some of the highest turnover rates with financial implications and harmful patient care. Turnover rates have increased during the COVID-19 pandemic because of the fear of getting sick, increased burnout, and job dissatisfaction.[9] Additionally, certain studies indicated that underrepresented racial minorities had higher rates of turnover, which may be because of exclusion from social networks and lack of institutional support.[8]

Strategies to improve retention and combat burnout have been described as the following five Cs (5Cs) of retention: communicate, connect, and collaborate, create learning opportunities, craft, and celebrate.[8] First, employers should communicate expectations and foster an environment where employees feel free to discuss potential areas for improvement.[8] A lack of good management or leadership is one of the main factors leading to nursing burnout and reasons for leaving the job, thus the employees should attempt to identify and address problems in advance.[4] The stay interview is a practice in which employers proactively meet employees to discuss factors causing employee dissatisfaction, and implement changes to prevent turnover.[8]

Next, employers should connect to know and understand their employees; this encourages collaboration.[8] Mentorship is an important mode to prevent the feeling of isolation in new employees or underrepresented minorities, and this has been evidenced to decrease turnover.[8] Compared to other medical fields, dermatology staff frequently require specialized training on techniques pertinent to dermatology as outlined above. Formal mentorship and training of new employees by the existing staff facilitates onboarding and creates camaraderie, which prevent turnover. Employers should also create learning opportunities and encourage continuous career development in clinical and relevant nonclinical subjects.[8] Employees must be given appropriate autonomy to craft their work experience to support their personal

and professional well-being. For example, if an employee has interest in a specific subspecialty of dermatology, then the person must be allowed to plan their schedule to increase exposure to that field. Finally, employees' accomplishments must be celebrated and rewarded publicly.[8] This includes events dedicated to recognizing outstanding employees as well as handing incentives.

CONCLUSIONS

Dermatologists, office managers, and staff in leadership positions involved in the hiring process must personalize these strategies to fit the requirements of their employees and clinical practice. With increased turnover of nonphysician dermatology staff and the anticipated rising demands as the dermatologic requirements of an aging population grow, it is important for dermatologists to be aware of how to improve employee recruitment, hiring, and retention. Optimizing these practices in hiring ancillary medical staff improves patient care and reduces costs if implemented appropriately.

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REVIEW

Pseudoxanthoma Elasticum-Like Changes: Associations and Underlying Mechanisms

Nohra Ghaoui, MD; Jihane Abou-Rahal, MD; Nourhane Nasser, MS; Mazen Kurban, MD; Ossama Abbas, MD

ABSTRACT

Pseudoxanthoma elasticum (PXE) is an inherited disorder characterized by degradation and fragmentation of elastic fibers and calcium deposits in the dermis. It clinically manifests as yellow papules or plaques in a cobblestone distribution or "plucked-chicken skin" appearance on the lateral neck and/or flexural areas. In addition, it can also affect the eyes, cardiovascular, and gastrointestinal systems. It is considered as the prototype of ectopic heritable mineralization disorders, usually diagnosed in the second decade of life. The majority of patients are sporadic but recessive, but pseudodominant autosomal forms have been described as well. Mutations affecting the ATP-binding cassette subfamily C member 6 (*ABCC6*) gene or gamma-glutamyl carboxylase (*GGCX*) gene lead to PXE. Accumulating evidence in the literature has found that numerous disorders may demonstrate cutaneous PXE-like clinical and/or histologic features without any other systemic evidence of PXE or any genetic documentation of inherited mutations. In this review, we aimed to highlight all the disorders that were reported to exhibit PXE-like clinical and/or microscopic changes and to discuss possible underlying mechanisms leading to such an overlap. (*SKINmed*. 2024;22:172–177)

Pseudoxanthoma elasticum (PXE) is an inherited multisystem disorder characterized by aberrant mineralization of soft connective tissues, especially elastic fibers of the skin, eye, and cardiovascular system.[1] Onset of clinical manifestations usually begins in late childhood or early adolescence.[2] Primary cutaneous features include small and yellowish papules that progressively merge into larger plagues of inelastic and yellowish leathery skin with predilection for flexural areas (Figure 1). Microscopy of affected skin typically exhibits fragmentation, clumping, and calcification of elastic fibers in the upper and mid dermis (Figure 1). While manifestations of the eyes include angioid streaks and bleeding from the choroidal vessels, mineralization of the arterial blood vessel leads to cardiovascular features such as intermittent claudication, hypertension, gastrointestinal bleeding, and, infrequently, myocardial infarction.

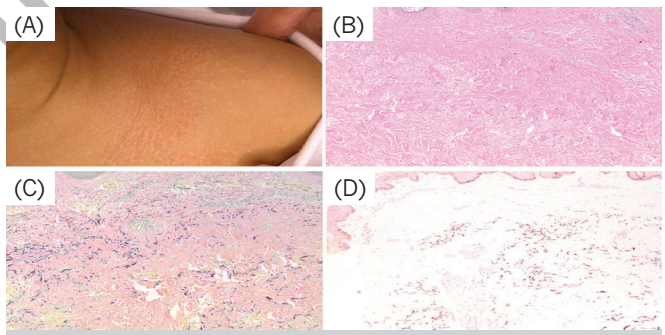

Figure 1. (a) Clinical illustration of PXE on the neck. (b) Histology of PXE exhibiting fragmentation, clumping, and calcification of elastic fibers in the upper and mid dermis (Hematoxylin and Eosin ×40). (c) Verhoeff–van Gieson staining (×100). (d) von Kossa staining (×100).

The majority of PXE patients are sporadic, but recessive autosomal and pseudodominant forms have been described as well.[3] The PXE locus is situated on the chromosome 16p13.1, and mutation affects the ATP-binding cassette subfamily C member 6 (*ABCC6*) gene, a member of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily. Digenic mutations have been described as well with the gamma-glutamyl carboxylase (*GGCX*) gene, explaining some variability in clinical phenotypes.[4–6] Actually, mutations in the *GGCX* gene caused an autosomal recessive PXE-like syndrome with coagulation deficiency in vitamin K-dependent clotting factors. Several phenotypes of this syndrome have been described depending on the associated

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Table 1. Cutaneous entities with PXE-like clinical and/or microscopic changes

Clinical and Microscopic PXE-like Changes	Clinical PXE-like Changes	Microscopic PXE-like Changes
Thalassemias (Beta, Delta-Beta, Beta/HbE)	Elastic fiber disorders (PDE, WFP, UDE, and late-onset FDE)	Lipodermatosclerosis
Sickle thalassemia	Penicillamine	Calciphylaxis and NFD
Sickle cell disease	Dermatomyositis	Localized acquired PXE
	Eosinophilia-myalgia syndrome (EMS)	Inflammatory dermatoses
		Neoplastic (basal cell carcinoma and hidradenoma)
		Miscellaneous (oral mucosa, lipedema, hydrophilic polymer vasculopathy)

FDE: focal dermal elastosis; NFD: nephrogenic fibrosing dermopathy; PDE: pseudoxanthoma elasticum-like papillary dermal elastolysis; PXE: pseudoxanthoma elasticum; UDE: upper dermal elastolysis; WFP: white fibrous papulosis of the neck.

ophthalmologic, cardiovascular, osseous, coagulation, and skin abnormalities, with the latter mimicking the cutaneous clinical and microscopic features of PXE.[4] As a matter of fact, the *GGCX* gene activates a number of proteins that play role in coagulation cascade as well as bone proteins affecting mineralization of the extracellular matrix, which could explain phenotypic findings in patients with mutations in this gene family.

Multiple disorders may demonstrate PXE-like clinical and/or histologic features.[7] While this overlap may create diagnostic difficulties, it may on other occasions serve as an indication to the diagnosis of those entities. The purpose of this review was to highlight all the disorders that mimic the cutaneous clinical and/or histopathologic features of PXE (Table 1) and discuss the possible underlying mechanisms that lead to such an overlap.

DISORDERS WITH BOTH CLINICAL AND MICROSCOPIC PXE-LIKE CHANGES

Thalassemia

Beta-thalassemia (β-thalassemia) patients are known to develop PXE-like changes in the skin, retina, or vessels at a higher frequency than the normal population.[8,9] In one study that included patients with homozygous or doubly heterozygous β-thalassemia, 20% had angioid streaks, 10% had angioid streaks and PXE-like skin lesions, and 26% had one or both clinical findings.[10] The findings were age-related, and 50% of patients aged more than 30 years had PXE-like changes whereas no patient aged less than 19 years presented any skin-related lesion. In another study, 16% of patients who had β-thalassemia presented with clinical PXE-like cutaneous changes, including yellow papules on the neck, axilla, elbows, groin, or other flexural areas.[8] Patients who had β-thalassemia and presented with PXE-like clinical symptoms revealed histopathologic findings similar to those found in classic inherited PXE in 100% of the patients.[11] Interestingly, some of these patients had a deletion for the alpha (α)-globin as well (4 out of 14 patients). These patients also indicated cardiac and vascular involvement similar to inherited PXE.

Multiple theories have emerged to try and elucidate the mechanisms leading to PXE-like changes in the skin of patients with β-thalassemia and other sickling syndromes. In fact, denatured hemoglobin membranes and free iron products induce oxidative and inflammatory reactions that affect red cell membranes, which, in turn, produce oxidative damage by plasma microparticles.[3] In addition, free radicals are produced excessively after reperfusion of occlusive tissue during sickling events. Not to mention, iron overload is a great source of oxidation, forming hydroxyl radicals leading to peroxidation of lipid and protein membranes.[12] All these mechanisms are believed to play a role in the structural destruction of elastin and elastic fibers. At the same time, one study found an increased plasma concentration of polymorphonuclear (PMN) elastase in patients with homozygous β-thalassemia, suggesting neutrophil activation leading to tissue damage via enzymatic granules containing myeloperoxidase and elastase.[13] PMN elastase inactivates its inhibitor, alpha-1 proteinase inhibitor, leaving it persistent at tissue damage translating into PXE-like manifestations both clinically and histologically. It is important to mention that PMN elastase levels were increased in all patients included in the study, regardless of whether they had PXE-like symptoms or not; thus, a causal pathogenetic mechanism cannot be established between PXE and neutrophil elastase. In addition, rare sequence variants were detected in the *ABCC6* and *ENPP1* genes in some thalassemic patients, both of which

were recognized as PXE-causing genes.[14] This also suggested another digenic inheritance theory for PXE manifestations, as already established for the *ABCC6* and *GGCX* genes.

Other Hemoglobinopathies

Presence of clinical and histologic manifestations of PXE has also been described in other hemoglobinopathies, such as delta-beta (δβ) thalassemia,[16] sickling disorders, sickle cell disease, and sickle thalassemia.[3] The skin's ocular and vascular components seem to have variable severity in these diseases with a tendency to appear in the second decade of life. Concurrently, these symptoms are considered acquired due to the oxidative process patients undergo in their primary disease.

DISORDERS WITH PXE-LIKE CLINICAL CHANGES

Elastic Fiber Disorders

Several elastic fiber disorders, including PXE-like papillary dermal elastolysis, white fibrous papulosis of the neck, upper dermal elastolysis (UDE), and focal dermal elastosis (FDE), may present with clinical cutaneous features of PXE; however, there are no associated systemic manifestations, and microscopic findings are different and allow differentiation from PXE.[17–21]

PXE-like papillary dermal elastolysis (PDE) is a rare acquired elastolytic disorder that usually affects women in late adulthood. It clinically presents with multiple yellow, symmetric, non-follicular papules coalescing into plaques on the neck, flexor forearms, axillae, or trunk with no associated systemic symptoms. Unlike PXE, histopathology reveals band-like loss of elastic tissues in the papillary dermis with no calcification and preservation of normal reticular dermal elastic fibers.[17–19,21]

Considered as an intrinsic manifestation of aging, white fibrous papulosis of the neck (WFP) usually presents as numerous, asymptomatic, symmetric, non-follicular, discrete, and 2–3-mm pale or white, oval or round papules mostly on the neck of middle-aged to elderly adults. Unlike PXE, white fibrous papulosis microscopically exhibits elastic tissue loss in the papillary and mid-reticular dermis with fibrosis and absence of calcification.[18,20]

Upper dermal elastolysis (UDE) is another rare disorder that clinically presents as small 2–5-mm papules on the neck, shoulders, and upper trunk. Its histopathology presents complete loss of elastic fibers in the upper papillary dermis commonly with associated elastophagocytosis and no calcification.[22,23]

Finally, focal dermal elastosis (FDE) or late-onset FDE is characterized by PXE-like asymptomatic yellow papular lesions on the neck, shoulder, back, or axillae; however, histopathologic focal increase is observed in normal-appearing elastic fibers instead of fragmentation or calcification usually observed in PXE.[24,25]

Penicillamine

Penicillamine, a heavy metal chelator, is used to treat many medical disorders such as Wilson's disease, cystinuria, and progressive systemic sclerosis. The prescribing of this drug has led to many consequences, including dermatologic complications such as hypersensitivity reactions, papulosquamous disorders, pemphigus/pemphigoid lesions, and PXE-like changes.[26] Penicillamine induces the development of yellow papules coalescing into a "plucked-chicken skin" appearance on the axillae and neck with redundant skin folds in the axillae and buttocks. It is responsible for an increase in the number of elastic fiber tissues with an irregular, saw-tooth, lumpy-bumpy appearance that displays multiple thorn-like projections along the papillary and reticular dermis. Unlike PXE, special stains do not reveal any calcific deposits in the elastic tissue.[27]

Others

Anecdotally, clinical PXE-like skin changes have also been described in association with dermatomyositis[28–30] and eosinophilia-myalgia syndrome (EMS).[31,32]

DISORDERS WITH MICROSCOPIC PXE-LIKE CHANGES

Lipodermatosclerosis

In a case series that included 25 patients with lipodermatosclerosis on their legs who underwent biopsy to characterize their disease, 21 patients established accumulation of von Kossa- and Verhoeff–van Gieson-positive basophilic elastic fibers with moth-eaten appearance in the deep septa.[33] There was partial replacement of the adipose tissue by fibrosis and widening of the septa. Fat necrosis and adipocyte dropout resulted in fat atrophy and pseudocyst formation. Foamy macrophages were also present and some of them formed lipogranulomas. Calcification of medium vessels and adipocytes was also seen in 13 patients. PXE-like septal elastosis with calcification was not pathognomonic but a consistent indication to diagnosis. Clinically, the lesions were tender plaques or nodules that were erythematous and indurated without any sign of cobblestoning or extension to other PXE classic areas such as the neck or trunk.[33,34] Scar formation and other fibrosing disorders were found to have a similar cytokine milieu with PXE, which could explain the presence of PXE-like fibers in lipodermatosclerosis.[35]

Calciphylaxis and Nephrogenic Fibrosing Dermopathy

Calciphylaxis is defined as metastatic calcification due to impairment of systemic calcium regulatory systems leading to calcification of vasculature and soft tissue.[36] Calcium deposits are found in small- and medium-sized vessel walls in the subcutis with consequent vascular thrombosis, ischemia, and necrosis. Clinically, calciphylaxis manifests as painful, erythematous skin changes with ulceration of lipid-rich areas. Calciphylaxis is further classified as uremic, mostly in end-stage renal disease and nonuremic, in different conditions such as hyperparathyroidism, neoplasms, alcoholic liver, and connective tissue diseases.[37] PXE-like changes are reported in the reticular dermis of the affected skin and in the subcutaneous fat, in both uremic and nonuremic patients of calciphylaxis.[38,39] In one case series that included biopsies from uremic and nonuremic patients of calciphylaxis, 46.2% revealed confirmed curled and frayed basophilic elastic tissue with calcific deposits in the subcutaneous tissue.[40] Interestingly, similar features were not observed in the dermis. Evidently, PXE-like changes (in the dermis or subcutaneous tissue) can be a helpful indication of calciphylaxis whenever the clinical diagnosis is unclear and may lead to early diagnosis and treatment of a potentially life-threatening condition.

Nephrogenic fibrosing dermopathy (NFD) usually occurs in the setting of chronic renal failure with hemodialysis. It clinically presents with symmetric skin sclerosis in the arms and legs and trunk and joint contracture. Histologically, increased collagen fibers are its characteristic. Rarely, PXE-like microscopic dermal elastic fiber calcification pattern has been documented in patients of concomitant NFD and calciphylaxis.[41] Such a change has been linked to the ability of CD34+ cells to contribute to fibrosis and calcification in NFD.[42–44]

Localized Acquired PXE

Localized acquired forms of PXE are also stated in the literature and are often named pseudo-PXE or perforating calcific elastosis.[45]

These lesions are asymptomatic hyperpigmented plaques, most often found around or superior to the umbilicus. These forms of PXE reveal on microscopically fragmented, basophilic elastic fibers in the mid and lower dermis.[46] On the one hand, a cell-mediated immunologic granulomatous reaction against actinic elastic fiber on sun-exposed areas can contribute to these microscopic features; on the other hand, genetically predisposed abnormal elastic fibers inducing a foreign body host reaction and a transepidermal elimination can induce this form of perforating dermatosis. Several factors contribute to the development of this disorder in the umbilicus region in genetically predisposed individuals, including abdominal trauma, multiparity, obesity, abdominal distension, abdominal surgery, chronic renal failure, and metabolic disorders.[47,48] Sometimes these factors also coincide with presence of the *ABCC6* gene mutation; a rare sequence variant, single heterozygous point mutation, was found in the *ABCC6* gene of a patient with pseudo-PXE without extracutaneous manifestations.[49]

Not all acquired forms are periumbilical. Acquired microscopic changes similar to PXE have been found at unremarkable and asymptomatic sites, such as the chin, with the sole presenting symptom of pruritus.[50,51]

Inflammatory Dermatoses

Although scarce, cutaneous PXE-like histopathologic changes have also been reported in patients with chronic inflammatory conditions such as autoimmune disorders and metabolic diseases, ranging from systemic lupus erythematosus (SLE), necrobiosis lipoidica, osteoectasia, granuloma annulare, lichen sclerosus, morphea profunda, erythema nodosum, and septal panniculitis.[33] These PXE-like changes were discovered in the deep dermis or subcutis, unlike classic PXE, and mostly manifested as destruction and thickening of elastic fibers with calcific elastic tissue.[52] It is interesting to mention that all reported patients were women. Concurrently with what was already mentioned, chronic inflammatory lesions seem to develop a milieu resembling that of scars and fibrosing processes leading to cytokine production necessary to the formation of PXE-like histopathologic changes.[35]

Neoplastic Entities

Cutaneous benign (hidradenoma) and malignant neoplasms (basal cell carcinoma) have been anecdotally described as potential triggers to adjacent PXE-like histopathologic reaction pattern. This reaction pattern could be the result of proteolytic substances induced by the tumor resulting in the alteration of normal mineral distribution and subsequent degeneration of elastic fibers.[34,53]

Others (Oral Mucosa, Lipedema, and hydrophyilic Polymer Vasculopathy)

In a prevalence study, specimens of oral mucosa biopsy established PXE-like connective tissue changes in around 10% patients. This was a higher prevalence than the suspected prevalence of PXE or the estimated prevalence of genetic mutation of the *ABCC6* gene.[54,55] In addition, anecdotal reports of PXE-like microscopic changes have been described in association with tumefactive hydrophilic polymer vasculopathy.[56]

CONCLUSIONS

In summary, multiple disorders may demonstrate PXE-like clinical and/or histopathologic features. While some disorders mimic PXE at both clinical and microscopic levels, other disorders may mimic either clinical or microscopic features of PXE. Being aware of such an overlap may help avoid misdiagnosis while at the same time such peculiar clinical or pathologic pattern could serve as an indication to the diagnosis of those entities.

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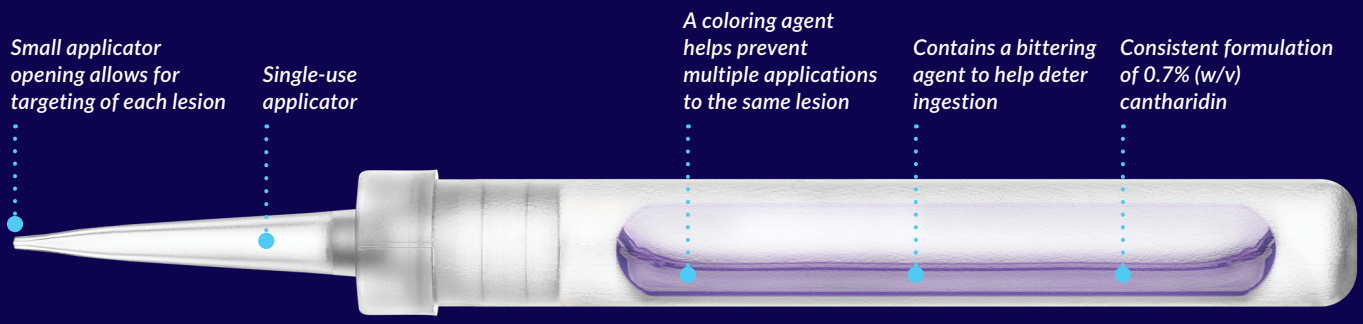

Adverse reactions were primarily mild to moderate local skin reactions at the application site, including vesiculation, pruritus, pain, discoloration, and erythema.[2]

Applicator is not to scale.

INDICATION

YCANTH (cantharidin) topical solution, 0.7% is indicated for the topical treatment of molluscum contagiosum in adult and pediatric patients 2 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS:

None.

WARNINGS AND PRECAUTIONS:

- YCANTH is for topical use only. YCANTH is not for oral, mucosal, or ophthalmic use. Life threatening or fatal toxicities can occur if YCANTH is administered orally. Avoid contact with the treatment area, including oral contact, after treatment. Ocular toxicity can occur if YCANTH comes in contact with eyes. If YCANTH gets in eyes, flush eyes with water for at least 15 minutes.
- Local Skin Reactions: Reactions at the application site may occur, including vesiculation, pruritus, pain, discoloration, and erythema. Avoid application near eyes and mucosal tissue, and to healthy skin. If YCANTH contacts any unintended surface, or healthy skin, immediately remove. If severe local skin reactions occur, remove prior to the recommended 24 hours after treatment.
- YCANTH is flammable, even after drying. Avoid fire, flame or smoking near lesion(s) during treatment and after application until removed.

ADVERSE REACTIONS:

The most common (incidence ≥1%) reactions are the following local skin reactions at the application site: vesiculation, pain, pruritus, scabbing, erythema, discoloration, application site dryness, edema, and erosion. Local skin reactions at the application site were observed in 97% of subjects treated with YCANTH during clinical trials. These local skin reactions are expected and related to the anticipated blistering response of the skin to cantharidin.

DRUG INTERACTIONS:

No studies evaluating the drug interaction potential of cantharidin have been conducted.

USE IN SPECIFIC POPULATIONS:

Pregnancy: There are no available data with use of YCANTH in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Given that systemic exposure to cantharidin following topical administration is low, maternal use is not expected to result in fetal exposure to the drug.

Lactation: Avoid application of YCANTH topical solution to areas with increased risk for potential ingestion by or ocular exposure to the breastfeeding child.

OVERDOSAGE:

Oral ingestion of cantharidin has resulted in renal failure, blistering and severe damage to the gastrointestinal tract, coagulopathy, seizures, and flaccid paralysis.

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To report SUSPECTED ADVERSE REACTIONS, contact Verrica Pharmaceuticals Inc. at 1-877-VERRICA (1-877-837-7422), or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. Local skin reactions are expected and should be reported if they are severe.

References: 1. Eichenfield LF, McFalda W, Brabec B, et al. Safety and efficacy of VP-102, a proprietary, drug-device combination product containing cantharidin, 0.7% (w/v), in children and adults with molluscum contagiosum: two phase 3 randomized clinical trials. *JAMA Dermatol*. 2020;156(12):1315-1323. doi:10.1001/jamadermatol.2020.3238 **2.** YCANTH (cantharidin) topical solution 0.7% Prescribing Information, Verrica Pharmaceuticals Inc., 2023.

Ycanth™ (cantharidin) TOPICAL SOLUTION 0.7%

Brief Summary
YCANTH™ (cantharidin) topical solution, 0.7%

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INDICATIONS AND USAGE

YCANTH is indicated for the topical treatment of molluscum contagiosum in adult and pediatric patients 2 years of age and older.

DOSAGE AND ADMINISTRATION

YCANTH is for topical use only and not for oral, mucosal, or ophthalmic use.

Important Administration Instructions and Dosage and Administration Overview:

- **See WARNINGS AND PRECAUTIONS and Dosage and Administration Instructions.**
- Use nitrile or vinyl gloves and eye protection during preparation and administration.
- **DO NOT** apply YCANTH near the eyes.
- **DO NOT** reuse the YCANTH applicator. The applicator is for a single treatment session only.
- **DO NOT** attempt to use a clogged applicator.
- **DO NOT** cut or modify the applicator in any way; doing so could reduce dispensing control.
- **DO NOT** remove the applicator cap prior to breaking the glass ampule.
- If any damage or leaks are observed on the applicator, applicators should be discarded in a sharps container and handled in accordance with accepted medical practice and applicable law. The YCANTH Break Tool should be managed as solid waste and placed in plastic recycling containers or the general trash.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Toxicities Associated with Inappropriate Administration: YCANTH is for topical use only. YCANTH is not for oral, mucosal, or ophthalmic use. Life threatening or fatal toxicities can occur if YCANTH is administered orally. Avoid contact with the treatment area, including oral contact, after treatment. Ocular toxicity can occur if YCANTH comes in contact with eyes. If YCANTH gets in eyes, flush eyes with water for at least 15 minutes.

Local Skin Reactions: Reactions at the application site may occur, including vesiculation, pruritus, pain, discoloration, and erythema. Avoid application near eyes and mucosal tissue, and to healthy skin. If YCANTH contacts any unintended surface, or healthy skin, immediately remove. If severe local skin reactions occur, remove prior to the recommended 24 hours after treatment.

Flammability: YCANTH is flammable, even after drying. Avoid fire, flame or smoking near lesion(s) during treatment and after application until removed.

ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: Local Skin Reactions.

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

YCANTH was studied in two randomized, double-blind, placebo-controlled phase 3 trials, Trial 1 (NCT03377790) and Trial 2 (NCT03377803) (n=266, and n=262, respectively) in subjects with molluscum contagiosum. Most patients received a single 24-hour dermal administration of YCANTH or vehicle for each lesion every 3 weeks for up to 4 treatments. YCANTH Solution or vehicle were removed prior to the 24-hour timepoint in 109/311 (35%) subjects treated with YCANTH Solution and 46/216 (21%) subjects treated with vehicle due to treatment-emergent adverse events.

Table 1 presents the percentage of subjects with selected adverse reactions (incidence ≥1%) by the most severe grade reported during Trial 1 and Trial 2. Adverse reactions were primarily local skin reactions at the application site. Local skin reactions at the application site were observed in 97% of subjects treated with YCANTH during both trials.

Table 1. Percentage of Subjects with Selected Adverse Reactions (Incidence ≥1%) by Severity in Trial 1 and Trial 2 (Safety Population)

	YCANTH N=311			Vehicle N=216		
Preferred Term Name	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**
Application site vesicles	60%	32%	4%	27%	2%	0%
Application site pain and pain	41%	20%	2%	16%	1%	0%
Application site pruritus and pruritus	47%	8%	1%	30%	7%	0%
Application site scab and scab	39%	9%	0%	20%	1%	0%
Application site erythema and erythema	24%	21%	<1%	20%	7%	0%
Application site discoloration	28%	4%	<1%	12%	1%	0%
Application site dryness	19%	2%	0%	14%	1%	0%
Application site edema	7%	3%	0%	3%	1%	0%
Application site erosion	6%	1%	0%	1%	0%	0%
Contact dermatitis	0%	1%	0%	0%	0%	0%

DRUG INTERACTIONS

No studies evaluating the drug interaction potential of cantharidin have been conducted.

USE IN SPECIAL POPULATIONS

Pregnancy: There are no available data with use of YCANTH in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Given that systemic exposure to cantharidin following topical administration is low, maternal use is not expected to result in fetal exposure to the drug.

Lactation: Avoid application of YCANTH topical solution to areas with increased risk for potential ingestion by or ocular exposure to the breastfeeding child.

Pediatric Use: The safety and effectiveness of YCANTH for the treatment of molluscum contagiosum have been established in pediatric patients aged 2 years and older. The use of YCANTH in pediatric patients is supported by results from adequate and well-controlled trials in patients 2 years of age and older; although the safety and efficacy of drug use for longer than 12 weeks has not been established. The safety and efficacy in pediatric patients below the age of 2 years have not been established.

Geriatric Use: YCANTH has not been studied in geriatric patients.

OVERDOSAGE

Oral ingestion of cantharidin has resulted in renal failure, blistering and severe damage to the gastrointestinal tract, coagulopathy, seizures, and flaccid paralysis.

PATIENT COUNSELING INFORMATION

Advise the patient and/or caregivers to read the FDA-approved patient labeling (Patient Information).

Manufactured by:
Pharmaceutical Packaging Solutions
341 JD Yarnell
Industrial Pkwy,
Clinton, TN 37716

For:
Verrica Pharmaceuticals Inc.
44 West Gay Street, Suite 400
West Chester, PA 19380

ORIGINAL CONTRIBUTION

Veganism in Dermatology: Special Considerations for the Vegan Hair Loss Patient

Maria Karim, BA;[1]* Elizabeth J. Klein, BA;[2]* Jamie Widawsky, PA-C, MPAS;[2] Jerry Shapiro, MD;[2] Kristen Lo Sicco, MD[2]

ABSTRACT

Veganism is a practice that promotes abstinence from all animal-derived products or foods. While veganism commonly refers to adopting a vegan diet, the term "veganism" also encompasses broader lifestyle practices. As veganism grows in popularity, patients often turn to their dermatologists for guidance regarding the identification of vegan ingredients in personal care and hair care products.[1] Additionally, several over-the-counter (OTC) and prescription medications recommended in the management of dermatologic conditions are often questioned about their applicability to veganism. We discuss the relevance of vegan diets to dermatologic clinical practice, address common questions relevant to patients, and offer guidance on how to identify vegan products. (*SKINmed*. 2024;22:180–186)

OFFICIAL CERTIFICATION OF VEGAN PRODUCTS

Although the definition of vegan may vary, it most commonly refers to wholly or partial abstinence from food or products derived from animals. V-label is an internationally recognized and registered symbol for labeling vegan and vegetarian products and services. V-label is not a federal regulating body, although this symbol is applied to the food, cosmetics, restaurant, and hospitality industries. Products applying for V-label certification must endure several stages of approval, as each ingredient is tested individually. In order to obtain V-label certification, products and services must meet guidelines developed and approved by European vegan and vegetarian associations. These guidelines are periodically updated according to evolving criteria for defining vegan.[2] V-label also requires that products do not undergo animal testing to be certified. Although many vegan products are also cruelty-free, this is not always guaranteed. Being cruelty-free ensures that a product and its ingredients or formulations are not tested on animals at any point during the development process. The Leaping Bunny program is an internationally recognized standard that grants certification for being cruelty-free or nonanimal-tested cosmetics and household products. Products certified by Leaping Bunny are guaranteed to be 100% free of new animal testing, ensuring that certified products will not undergo animal testing in the future.[3]

HOW TO IDENTIFY VEGAN PRODUCTS

Although the V-label is an excellent reference for identifying vegan products, some products may not be V-label-certified or are not labeled clearly. While reading the full ingredient lists of products, consumers must be aware of common animal-derived ingredients that must be avoided in vegans. When specifically looking for vegan hair care and beauty products, traditional animal-derived ingredients, such as honey, collagen, gelatin, lanolin, and beeswax, are not included; however, there could be many lesser-known animal-derived common ingredients. A comprehensive list of common animal-derived ingredients used in hair care and personal care products is included in Table 1 for reference.

ORAL SUPPLEMENTS AND THERAPIES COMMON AMONG HAIR LOSS PATIENTS: WHAT MAKES THEM VEGAN?

Dietary supplements are often recommended by dermatologists for managing the hair, skin, and nail disorders in patients with

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Table 1. Common Animal-Derived Ingredients in Personal Care Products

Alanine	Egg protein	Polypeptides
Albumen/albumin	Elastin	Polysorbates
Allantoin, alcloxa, aldioxa	Emu oil	Pristane
Aliphatic alcohol	Estrogen, estradiol	Progesterone
Alpha-hydroxy acids (AHAs)	Fatty acids	Provitamin A
Ambergris	Feathers	Retinol
Amerchol L101	Fish oil	Ribonucleic acid (RNA)
Amino acids	Fish scales	Sable brushes
Aminosuccinate acid, Aspartic acid	Gelatin	Shark liver oil
Animal fats and oils	Glycerin, glycerol, glycreth-26	Shellac
Arachidonic acid	Guanine pearl essence	Silk powder
Arachidyl propionate	Honey	Snails
Bee pollen	Hyaluronic acid	Spermaceti
Beeswax (Cera Flava), honeycomb	Hydrolyzed animal protein	Squalene
Biotin, vitamin H, vitamin B factor	Keratin	Stearic acid
Boar bristles	Lactic acid	Stearyl alcohol
Calciferol	Lactose	Steroids, sterols
Caprylic acid, capryl amine oxide, capryl betaine, caprylic triglyceride	Lanolin, lanolin acids, lanosterols	Tallow
Carmine, cochineal, carminic acid	Lard	Turtle oil
Carotene, provitamin A, beta-carotene	Lecithin	Tyrosine
Casein, caseinate, sodium caseinate	Linoleic acid	Urea
Castor, castoreum	Lipids	Vitamin A
Cerebrosides	Marine oil	Vitamin B12 (cobalamin)
Cetyl alcohol	Methionine	Vitamin D
Cetyl palmitate	Milk protein	
Chitosan	Mink oil	
Cholesterin	Monoglycerides	
Cholesterol	Musk oil	
Civet	Myristic acid	
Cod liver oil	Nucleic acids	
Collagen	Octyldodecanol	
Colors/dyes	Oleic acid	
Cysteine, L-form	Palmitic acid	
Cystine	Panthenol	
Duodenum substances	Placenta, placenta polypeptide	

nutritional deficiencies. Managing patients with hair loss (alopecia) often results in recommending therapies that may partially be animal-derived. While evaluating patients presenting with hair loss, levels of vitamin D, zinc, and ferritin are often obtained in addition to complete blood count, complete metabolic panel, and thyroid function testing. If nutritional deficiencies are identified, and supplementation is recommended, dermatologists and patients must be aware that not all over-the-counter formulations of vitamins and minerals are created uniformly in their ingredients. In this paper, the authors review different supplements and hair loss therapies that may contain animal-derived ingredients that dermatologists must be cognizant of when treating vegan patients.

Vitamin D

Vitamin D supplements are found in the form of vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). While vitamin D2 is most often suitable for vegans, it is considerably less potent than its D3 counterpart.[4] Alternatively, vitamin D3 supplements may be derived from an animal source. Vitamin D3 may come from an animal source, such as lanolin (a wax secreted by the sebaceous glands of wooly animals), or lichen (a vegan-friendly source).[5,6] Until recently, most vitamin D supplements were produced from lanolin.[7] Lanolin is formed as a by-product of wool-farming, as crude lanolin is extracted via scouring of the wool and purified via saponification.[8] Crude cholesterol is then derived from lanolin alcohols through solvent washings and column chromatography until it is purified and crystalline.[9] Upon exposure to ultraviolet (UV) radiation, lanolin oil, derivative of 7-dehydrocholesterol, transforms into cholecalciferol. Alternatively, lichens are a type of algae that produce vitamin D naturally in response to UV-B exposure as a protective mechanism against UV radiation of the sun.[10] This is a plant-based source of vitamin D3; therefore, a lichen-derived vitamin D3 supplement must be recommended for vegan patients starting vitamin D supplementation.

Iron

Iron exists in two main forms—heme iron and non-heme iron. Heme iron is found primarily in animal products, such as beef, pork, chicken, and fish. Non-heme iron is found in green leafy vegetables, legumes, nuts, seeds, fortified cereals, eggs, and dairy.[11] Non-heme iron is less well-absorbed, compared to heme iron.[12] Vegans only consume non-heme iron, which may account for the lower serum levels of iron in plant-based patients, compared to non-vegans.[13] Most iron supplements are synthesized chemically and contain iron gluconate or iron sulfate, which are non-heme sources suitable for a vegan diet.

Saw Palmetto

Saw palmetto (*Serenoa repens*) is derived from the berries of the American dwarf tree. The extract consists of phytosterols, fatty acids, B-carotene, and polysaccharides.

It has been proven to inhibit both type 1 and type 2 5α-reductase halting the conversion of testosterone into dihydrotestosterone (DHT).[14] Saw palmetto extract also prevents DHT uptake in target cells and reduces DHT-androgen receptor binding by approximately 50%.[15] Topical and oral saw palmetto in supplements may have some efficacy in treating androgenetic alopecia (AGA) due to its antiandrogenic properties.[15,16] Although high-quality studies have not yet supported its efficacy in treating alopecia, it is a plant-derived option suitable for vegan patients.[16] Vegan patients must be conscious of other vitamins, minerals, or chemical additives that may be incorporated into saw palmetto formulations.

Rosemary Oil

Rosemary oil (*Rosmarinus officinalis*) is a medicinal plant comprising caffeic acid, rosmarinic acid, camphor, and 12-methoxycarnosic acid. It is postulated to function as an anti-inflammatory and antioxidant agent.[15] A randomized controlled trial (RCT) comparing the efficacy of twice-daily application of rosemary oil in AGA patients determined that it was comparable to the same application of minoxidil 2% solution applied for 6 months.[17] Rosemary oil thus presents a vegan option that could be efficacious in AGA patients.

Pumpkin Seed Oil

Pumpkin seed oil (*Cucrubita pepo* L.) comprises several saturated and unsaturated fatty acids and is thought to have antioxidant, anti-inflammatory, and antimicrobial properties.[18] A major constituent of pumpkin seed oil is linolenic acid, which may inhibit 5α-reductase and increase hair growth.[15] A double-blind RCT evaluating the efficacy of applying daily 400-mg of pumpkin seed oil (PSO) in treating AGA in men established a 40% increase in hair count after 24 weeks of treatment ($P < 0.001$).[19] A randomized comparative trial assessing the efficacy of once daily application of topical pumpkin seed oil versus topical minoxidil 5% also revealed promising results;[18] hence, topical and oral pumpkin seed oil is a vegan-friendly option for treating AGA.

Topical Minoxidil

Topical minoxidil is a common therapy recommended for treating both non-scarring and scarring types of alopecia. Although formulations may vary according to brands, generic topical minoxidil solution most often contains minoxidil in concentrations

of 2% or 5%, ethanol, propylene glycol, and purified water.[20] These ingredients are generally considered to be vegan; however, patients must be judicious in checking for additional or alternative ingredients in formulations, which may be animal-derived. For example, patients allergic to propylene glycol may choose to have minoxidil solution formulated with glycerin. Glycerin is a by-product of hydrolysis of fats and oils, and is derived from animal fats, vegetable sources, or manufactured synthetically.[21] Glycerin functions as a denaturant, fragrance ingredient, hair conditioning agent, and viscosity-decreasing agent.[21] Topical minoxidil 5% is also available in a foam formulation with inactive ingredients, including butane, glycerol, butylated hydroxytoluene, cetyl alcohol, citric acid, dehydrated alcohol, lactic acid, isobutane, polysorbate 60, propane, stearyl alcohol, and purified water. Lactic acid is another ingredient found in topical minoxidil foam. Although lactic acid is a by-product of fermented dairy products or meat, it may also be derived from plant-based sources, such as beet sugar, potatoes, and corn starch, or synthesized chemically.[22] Cetyl alcohol is a compound initially isolated as a product of spermaceti, a waxy substance from the head cavities of sperm whale oil.[23] Recent concerns over the extinction of sperm whale has shifted modern production toward utilizing vegetable, coconut, or palm oil as a source of cetyl alcohol. Palm oil, although vegan, is avoided by many vegans due to its contribution to climate change and orangutan extinction.[24] If listed as ingredients in minoxidil solutions, patients must clarify the source of the glycerin, lactic acid, and cetyl alcohol, as they may vary among manufacturers.

Ketoconazole Shampoo

Ketoconazole shampoo is commonly prescribed for managing seborrheic dermatitis of the scalp. Ketoconazole may also carry anti-androgen properties by inhibiting 5α-reductase and the androgen receptor, potentiating its possible utility in treating AGA.[25,26] Although ketoconazole is the main active ingredient in ketoconazole shampoo, patients and dermatologists must be aware of added inactive ingredients as well. Inactive ingredients include acrylic acid polymer, butylated hydroxytoluene, cocamide monoethanolamine (MEA), food drugs and cosmetics Blue #1, fragrance, glycol distearate, polyquaternium-7, quaternium-15, sodium chloride, sodium cocoylsarcosinate, sodium hydroxide, hydrochloric acid, sodium laureth sulfate, tetrasodium ethylenediaminetetraacetic acid (EDTA), and water.[27] Of these, it is most important for vegans to be aware of glycol distearate. Glycol distearate is a pearlescent thickener, may or may not be a vegan, as it is a glycol compound of stearic acid, and may be animal-derived from cows or hogs (Table 1). Vegan sources of glycol distearate originate from soybean oil or canola oil.[28]

Thyroid Supplements

Thyroid supplementation is commonly recommended for patients found to have clinical hypothyroidism while undergoing evaluation for hair loss. Thyroid supplementation exists in two main forms—dessicated and synthetic. Dessicated thyroid replacement therapy, which is derived from the animal thyroid gland (often derived from pigs), is dried and powdered for medicinal use.[29] Armor is a type of dessicated thyroid medication which is not vegan. Synthetic thyroid supplementation is currently produced and more commonly recommended for use.[30] For example, Cytomel® is a synthetic version of triiodothyronine (T3), which is often vegan, although it may contain corn starch, gelatin, and stearic acid.[31] Alternatively, Synthroid® is a synthetic version of thyroxine (T4); however, it is formulated with corn starch and lactose, which preclude its applicability to a vegan diet.[32] Vegan patients diagnosed with hypothyroidism must therefore opt for synthetic thyroid replacement, and be cautious of additives.

Oral Minoxidil

Low-dose oral minoxidil is becoming increasingly popular for treating both non-scarring and scarring forms of alopecia due to its established efficacy and well-described safety profile.[33] Inactive ingredients contained in oral minoxidil formulations include cellulose, corn starch, lactose, magnesium stearate, and silicone dioxide.[34] Lactose is found in dairy products of mammals and often used in medications as a carrier to reduce drug particle aggregation and improve particle flow. It also acts as a stabilizer to ensure the medication retains its properties until consumption (Table 1).[35] Magnesium stearate is incorporated into medications as a filler or a lubricant coat to aid in swallowing. It is a derivative of stearic acid, a fatty acid found in pork, butter, chicken, beef, fish, or milk, or in cocoa, grains, palm, coconut, or vegetable oil.[36] The source of magnesium stearate as well as the production process of corn starch must be clarified for vegan patients.

Oral Finasteride

Oral finasteride is an inhibitor of type 2 5α-reductase, and is approved by the US Food and Drug Administration (FDA) for treating AGA in men.[37] Inactive ingredients which may be found in finasteride tablets include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, sodium starch glycolate, hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, magnesium stearate, talc, docusate sodium, and yellow and red ferric oxide.[38] Similar to oral minoxidil tablets, vegan patients must be aware of lactose monohydrate and magnesium stearate.

Oral Dutasteride

Dutasteride is a potent inhibitor of both type 1 and type 2 5α-reductase, effectively preventing the conversion of testosterone to 5α-dihydrotestosterone.[39] Oral dutasteride is formulated as gelatin capsules containing a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The capsules contain gelatin from bovine spongiform encephalopathy-free bovine sources, glycerin, and yellow ferric oxide.[40] Caprylic acid may be derived from goat, cow, or sheep milk, or from vegan sources, such as coconut, palm, or other plant oils (Table 1). Glycerin is another inactive ingredient in oral dutasteride, and may be animal- or plant-derived, as it is a by-product of hydrolysis of fats and oils.[21] Glycerin functions as a denaturant, humectant, and viscosity-decreasing agent, and may be incorporated in hair conditioners, fragrances, or oral medications.[21] Vegan must be aware of gelatin for being an important ingredient of cosmetics, foods, and medications. It is a purified animal protein derived from pig skin, cattle hides and bones, or fish skins.[41] Gelatin can be manufactured by boiling collagen derived from the skin, bones, teeth, or tendons of animals.[42]

Shampoos and Conditioners

As veganism becomes more popular, the demand for vegan hair care products has increased. While some hair care products may be clearly labeled as vegan, consumers must be aware of avoiding potentially animal-derived ingredients. Amino acids, bee pollen, biotin, carmine, cholesterol, egg protein, ground feathers, gelatin, guanine, hydrolyzed animal protein, keratin, lecithin, milk protein, myristic acid, nucleic acids, palmitic acid, panthenol, placenta polypeptides, propolis, RNA, spermaceti, stearyl alcohol, and urea are common animal-derived ingredients that may be incorporated into shampoo formulations. In particular, keratin and biotin are popular ingredients of shampoos marketed to offer hair strengthening properties.

Keratin is a major constituent of the human hair and forms an expansive cross-linked network of disulfide bonds, resulting in a strong hair shaft.[43] It is derived from the hooves, hair, wool, feathers, and skin of animals when incorporated into hair care products.[44] Biotin can be animal-derived or vegan. It is sourced from liver and kidney meat, egg yolk, legumes, nuts, seeds, mushrooms, avocados, yeast, sweet potatoes, and cow milk, although over-the-counter hair care products often contain synthetic biotin.[45] Milk protein, nucleic acids, stearic acid, and steroids may be found in non-vegan conditioning products (Table 2). Steroids, which include sterols, can be derived from animal glands or plant tissues and, due to their emulsifying properties, are thought to restore and strengthen damaged hair shafts when incorporated into hair conditioning products.[46,47]

Table 2. Common Animal-Derived Ingredients in Shampoos and Conditioners

Amino acids	Hydrolyzed animal protein	Propolis
Bee pollen	Keratin	Ribonucleic acid (RNA)
Biotin	Lecithin	Spermaceti
Carmine	Milk protein	Stearic acid
Cholesterol	Myristic acid	Stearyl alcohol
Egg protein	Nucleic acids	Steroids
Ground feathers	Palmitic acid	Urea
Gelatin	Panthenol	
Guanine	Placenta polypeptides	

CONCLUSIONS

As veganism grows in popularity and presence, dermatologists are frequently considering the applicability of medical therapies and personal care products to a vegan lifestyle. This is especially relevant when managing vegan patients presenting with hair loss, as many recommended supplements and hair care products are derived from animals. Both vegan patients and dermatologists must judiciously evaluate the source of ingredients of medical therapies and personal care products prior to use by the vegan population.

CONFLICTS OF INTEREST

Dr. Shapiro is a consultant for Aclaris Therapeutics, Incyte, and Replicel Life Sciences. Drs. Shapiro and Lo Sicco were investigators for Regen Lab and are investigators for Pfizer. Dr. Lo Sicco is a consultant for Pfizer.

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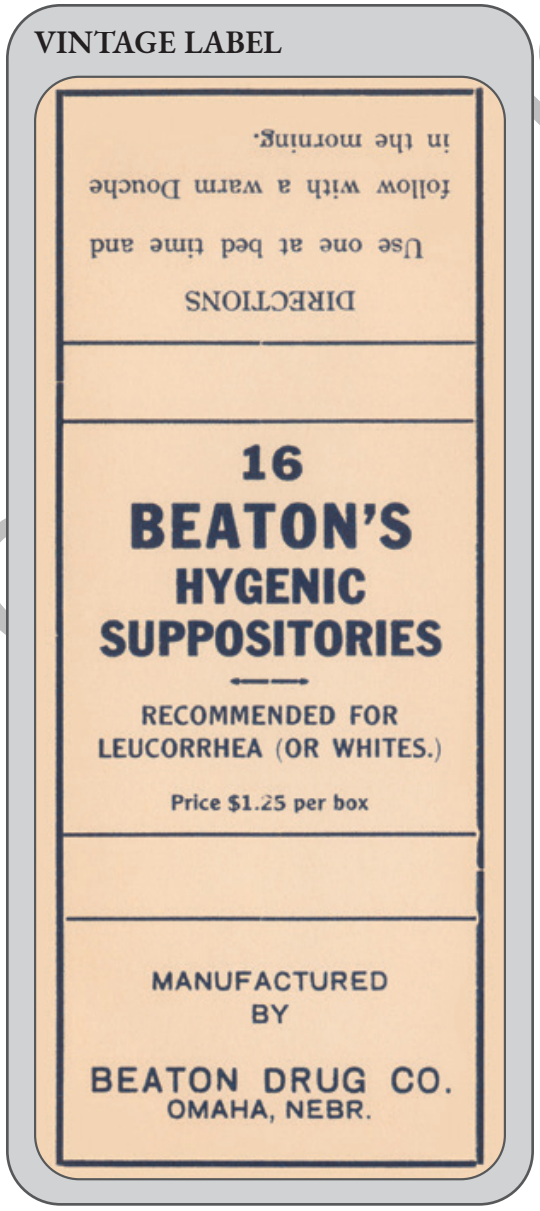

ORIGINAL CONTRIBUTION

Clinical Evaluation of the Efficacy of Itch-Relief Moisturizers Containing Maltotetraose for Dry, Itchy, and Sensitive Skin

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ABSTRACT

Itching is a prominent clinical manifestation of sensitive skin; it reduces cutaneous barrier function, mainly caused by dryness. Scratching to relieve itching destroys the skin barrier, thus forming the itch–scratch cycle that results in additional disruption of skin barrier and chronic itching. Treatment involves alleviation from itching for sensitive skin. Recently, substance P (11-amino acid neuropeptide of the tachykinin family) and neurokinin 1 receptor (NK1R) have been considered to provide a key pathway to treat chronic itching. A single-center, open-label study was conducted comprising subjects with dry, itchy, and sensitive skin to evaluate the efficacy of two types of itch-relief moisturizers, mist and lotion, containing maltotetraose (MTO). In all, 35 subjects used mist containing MTO, resulting in significant improvement in itch score from 1 minute to 2 hours following single application. On the other hand, 34 subjects applied lotion containing MTO for 1 week, resulting in significant improvement in itch score, skin hydration, and clinical scores of erythema/redness and dryness; however, in both cases, improvement was not observed in the measurement of transepidermal water loss (TEWL). It was concluded that two types of itch-relief moisturizers containing MTO were effective for dry, itchy, and sensitive skin. (*SKINmed*. 2024;22:187–196)

Itch, or pruritus, is defined as an "unpleasant sensation which triggers desire or urge to scratch."[1] Itch can have multiple factors, including common dermatologic disorders, atopic dermatitis (AD), contact dermatitis, psoriasis, etc. Itching has been reported to be a prominent clinical manifestation of sensitive skin,[2] which is an independent syndrome, although it can be associated with AD, another skin disease, or an atopic predisposition.[3] In 2016, a special interest group from the International Forum for the Study of Itch defined sensitive skin as a syndrome characterized by the appearance of unpleasant sensations (stinging, burning, pain, pruritus, and tingling sensations) in response to stimuli, such as water, cold, heat, or other physical and/or chemical factors, that would not normally cause a reaction.[4] The pathophysiology of sensitive skin is still poorly understood. Compared to the normal population, subjects with sensory irritation tend to have a less hydrated, less suppled, more erythematous, and more telangiectatic skin. In particular, significant differences were determined for erythema and hydration/dryness.[5] This low epidermal barrier allows entry of irritants and itch-causing agents, such as bacterial proteases, allergens, and mechanical irritation, and fails to adequately protect nerve endings.[6,7] Nerve endings have various kinds of receptors related to itching, which result in itching with irritation. People scratch the skin to release itching; however, scratching leads to the secretion of itching factors, such as histamine, substance P (SP; 11-amino acid neuropeptide of the tachykinin family), and various inflammatory cytokines, thus inducing the consequent scratching behavior. This long-term itching, resulting in the itch–scratch cycle, imparts a severe and significant impact on patient's quality of life.[8–10] As a treatment for sensitive skin, moisturizers and optimized lipid mixtures are used to improve the barrier function;[11] however, it is believed that itching must be treated as soon as possible so as not to aggravate the skin condition.

Regarding itching pathways, the following two subtypes of itch-sensitive neurons are recognized that are entirely separate and independent: histaminergic neurons and nonhistaminergic

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neurons.[12] Histamine is a well-known itching factor, and antihistamines are commonly used as antipruritic agents; however, antihistamines do not relieve chronic itching in patients with AD, psoriasis, or other dermatologic disorders,[12–14] and the available treatment options for chronic itching are inadequate. A nonhistaminergic pathway appears to play a larger role in conditions associated with chronic itching;[15,16] in particular, substance P and neurokinin 1 receptor (NK1R) play an important role in itch signaling and may be a rational target for addressing chronic itching.[17,18] Substance P is a neuropeptide comprising 11 amino acid residues. It is secreted and released by sensory nerve terminals because of various stimuli. The released substance P binds with NK1R, which is expressed on sensory nerves, specifically the C-nerve fibers, and its signal is subsequently transmitted from these neurons to other neurons in the brain. NK1R also expresses epidermal keratinocytes and through binding with substance P leads to an additional increase in itching promoted by the secretion of substance P, nerve growth factor, and various inflammatory cytokines.[17]

We considered substance P and NK1R as new targets for breaking the itch–scratch cycle and initiated development of daily skin care products for dry, itchy, and sensitive skin. We first examined effective materials for inhibiting NK1R activation by calcium imaging. As a result, we found maltoteraose (MTO) to be effective for inhibiting NK1R activation.[19,20] MTO is produced from corn starch by enzymatic reaction, in which glucose with α-1,4-glycosidic bond is attached, and is a safe material used commonly as a sweetener in foods. MTO contains more hydroxyl groups than other humectants, such as butylene glycol and glycerin, resulting in a greater hydration effect. Based on these facts, we proposed that MTO could be an effective material for skin care products, which can both suppress itching and increase hydration, thus improving skin barrier function of sensitive skin. Concerning the effective amount of MTO, internal data indicated that 1.0% MTO was effective to treat dryness and itching;[19,20] therefore, we included 1.0% MTO in proposed test agents.

People with sensitive skin can have itching throughout the day, and because skin itching often becomes worse in dry and cold climate[11] (e.g., at the office), we conceived to offer skin care products that were easy to use, and were suitable to relieve itching throughout the day.

We developed two types of itch-relief moisturizers containing MTO. The first moisturizer was a portable mist which provided quick relief from itching and suppressed scratching behaviors. The second moisturizer was a lotion developed to improve the barrier function of the stratum corneum with suppression of itching through continuous use.

In the present study, we examined the efficacy of these two types of itch-relief moisturizers containing MTO in individuals who had self-perceived sensitive and dry skin, and had itching because of dryness.

MATERIALS AND METHODS

Study Design and Subjects

Efficacy Evaluation of Mist

The test agent was applied at the itching site, either on the arm, leg, thigh, or trunk, and was evaluated via self-assessment of itching intensity and consumer perception questionnaires. In all, 60 patients were enrolled in the study. After a washout of 7 days, 35 patients, aged 25–65 years, and who had met all the inclusion criteria and none of the exclusion criteria, were selected for study participation. Table 1 shows the inclusion and exclusion criteria for the efficacy evaluation of mist.

Efficacy Evaluation of Lotion

The test agent was applied for 2 weeks at the itching site of the lower leg. Dermatologist's evaluation (erythema/redness and dryness), self-assessment of itching intensity, instrumental measurements, and consumer perception questionnaires were evaluated. In all, 51 patients were enrolled for study participation. The duration of washout was 7 days. A total of 35 patients, aged 23–59 years, who met all the inclusion criteria and none of the exclusion criteria, were selected for the efficacy evaluation of lotion. Table 2 shows the inclusion and exclusion criteria for the efficacy evaluation of lotion.

Efficacy Evaluation of Mist and Efficacy Evaluation of Lotion have been tested on different subjects with different Criteria.

Ethical Approval

Investigational test products, study protocol, informed consent form, subject recruitment material, and written instructions of the study were reviewed and approved by the Human Research Ethics Committee, IntegReview (renamed Advarra; IRB00004920 and IRB00001035). Informed consent was obtained from all the subjects prior to study initiation.

Settings

The tests were performed by Eurofins|CRL Inc. (CRL) in the United States, complying the applicable standards of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the Guidelines for Good Clinical Practice (GCP). The mist

Table 1. Inclusion and Exclusion Criteria for Efficacy Evaluation of Mist

Inclusion criteria

- Subject is a man or a woman aged between 20 and 65 years.
- Subject's ethnicity must be specified and listed in the subject demographic form.
- Subject has self-perceived sensitive skin.
- Subject has at least mild dryness of the skin according to a 5-point grading scale on the basis of dermatologist evaluation at baseline.
- Subject feels itchy somewhere on the body during the baseline visit. The itch occurs because of significant dry skin, which is confirmed by a registered nurse.
- Subject agrees to discontinue the use of OTC itch relievers on test sites once enrolled for the conditioning phase and during the study period.
- Subject agrees to discontinue the use of cosmetic itch relievers for the conditioning phase and for the study duration.
- Subject agrees to refrain from using a washing tool, such as scrub brush or loofah, for the study duration.
- Subject is willing to refrain from tanning and swimming for the study duration.
- Subject agrees not to start a new exercise program for the study duration.
- Subject agrees not to introduce any new cosmetic or toiletry products during the study.
- Subject is dependable and able to follow directions as outlined in the protocol.
- Subject is willing to participate in all study evaluations.
- Subject is in generally good health and has a current Panelist Profile Form on file at CRL.
- Subject has completed an authorization form of Health Insurance Portability and Accountability Act (HIPAA) conforming 45 CFR parts 160 and 164.
- Subject understands and is willing to sign an informed consent form conforming 21 CFR part 50: "Protection of Human Subjects."
- Subject is willing to be sequestered in laboratory for 2½ hours.

Exclusion criteria

- Woman subject is pregnant, nursing, planning a pregnancy, or not using adequate birth control methods.
- Subject has dermatitis on the test site.
- Subject has severe itch with noticeable abrasions (as determined by the principal investigator or sub-investigator).
- Subject has hives.
- Subject uses a prescribed itch reliever.
- Subject has received treatment with sympathomimetics, antihistamines, vasoconstrictors, non-steroidal anti-inflammatory agents, and/or systemic or topical corticosteroids within 1 week prior to initiation of the study.
- Subject has a history of acute or chronic dermatologic, medical, and/or physical conditions that would preclude application of the test material and/or could influence the outcome of the study.
- Subject is currently taking certain medications that, in the opinion of the principal investigator, could interfere with the study.
- Subject has known allergies to skin treatment products or cosmetics, toiletries, and/or topical drugs.
- Subject has a history of skin cancer or is currently undergoing treatment for active cancer of any type.
- Subject has insulin-dependent diabetes.

study was conducted from January 21, 2020 to January 29, 2020 whereas the lotion study was conducted from January 29, 2020 to March 2, 2020.

Test Agents

The mist (pH 5.7) was a formulated water base that contained 1.0% MTO and 0.3% menthol as active antipruritics. The lotion (pH 5.9) was a formulated emulsion base that contained 1.0% MTO as an active antipruritic.

Procedure

Efficacy Evaluation of Mist

The study procedure for mist is shown in Figure 1. After a 7-day washout period, during which patients were instructed to use the provided nonmoisturizing soap only (Purpose gentle cleansing bar), the patients reached the testing facility on the day of the study and entered the environment chamber having an approximate temperature of 20°C and 50% relative humidity (RH) for 15 minutes. Dryness of the test site was examined by a dermatologist, and subjects with at least mild dryness continued in the study. Subjects reported their itching sensation, and the results were recorded by the study staff using a 10-cm visual analog scale (VAS), which served as a baseline score. Then, the mist was applied by the study staff. Subjects self-assessed their itching sensation at the following time points: immediately after applying the mist; then after 1, 2, 5, 10, and 30 minutes, and 1 and 2 hours of application. Subjects' self-assessments were recorded by the study staff using a 10-cm VAS. Finally, a consumer perception questionnaire was completed by all subjects.

Efficacy Evaluation of Lotion

The study procedure for lotion is shown in Figure 2. After a 7-day washout period, during which patients were instructed

Table 2. Inclusion and Exclusion Criteria for the Efficacy Evaluation of Lotion

Inclusion criteria

- Subject is a man or a woman aged between 20 and 59 years.
- Subject has to possess the Fitzpatric skin type I–VI, which is recorded in demographic forms.
- Subject has to possess self-perceived sensitive skin.
- Subject must have mild to moderate itching (2.5–7.4 cm on the 10-cm VAS scale) on the lower legs because of dryness for at least at one time daily, and must feel itch at the time of the first visit/screening and during the baseline visit.
- Subject has mild to moderate (1 or 2 point as per the 7-point erythema/redness/dryness grading scale) dryness and redness on the lower legs.
- If enrolled, subject agrees not to shave/wax/remove hair from the lower legs during the conditioning phase and the study duration.
- Subject agrees not to wash or moisturize the test sites after application at baseline up to 24 hours.
- Subject is willing to refrain from the use of washcloths, loofahs, or coarse sponges on the lower legs.
- Subject is willing to refrain from tanning and swimming during the study period.
- Subject agrees not to start a new exercise program for the study duration.
- Subject agrees to wear apparel that easily allows access to the lower legs at all study visits to avoid rubbing of the lower legs when rolling up the trousers.
- Subject agrees not to wear pantyhose at all study visits.
- If subject uses OTC itch relievers, he/she must agree to discontinue use on the lower legs but may continue use on other parts of the body.
- Subject agrees not to introduce any new cosmetic or toiletry products during the study.
- Subject is dependable and able to follow directions as outlined in the protocol.
- Subject is willing to participate in all study evaluations.
- Subject is generally in good health and has a current Panelist Profile Form on file at CRL.
- Subject agrees to sign a photography release form, providing consent for capturing digital images for use in relation to this clinical study.
- Subject has completed an HIPAA authorization form conforming 45 CFR parts 160 and 164.
- Subject understands and is willing to sign an informed consent form conforming 21 CFR part 50: "Protection of Human Subjects."

Exclusion criteria

- Woman subject is pregnant, nursing, planning a pregnancy, or not using adequate birth control methods.
- Subject experiences repeated scratching that has caused raised areas on the skin that may bleed or become infected because of the intense nature of itch (as determined by the principal investigator or sub-investigator).
- Subject has hives.
- Subject has dense hair on the lower legs.
- Subject is a regular user of prescribed itch relievers.
- Subject has used cosmetic itch relievers on the lower legs within 1 week prior to the start of the study.
- Subject is currently taking certain medications or oral supplements, such as systemic or topical corticosteroids, anti-inflammatory drugs, or retinoid medications or products, which in the opinion of the investigator, could influence the outcome of the study or interfere with study observations.
- Subject has known allergies to skin treatment products or cosmetics, toiletries, and/or topical drugs.
- Subject exhibits sunburn, eruptions, abrasions, burn marks, etc., on the test sites or has tattoos or piercings that might interfere with study evaluations.
- Subject exhibits or reports a history of acute or chronic dermatologic, medical, and/or physical conditions that would preclude application of the test material and/or could influence outcome of the study.
- Subject has participated in a clinical study that involved the legs within 1 week prior to initiation of this study.
- Subject has a history of skin cancer or is currently undergoing treatment for active cancer of any type.
- Subject has insulin-dependent diabetes.

to use the provided nonmoisturizing soap only (Purpose gentle cleansing bar), the subjects reached the testing facility on the day of the study wearing loose apparel that did not rub or scratch the lower legs when rolled up and removed long and tight boots. Subjects entered the environment chamber having an approximate temperature of 20°C and 50% R.H. They washed their lower legs under the supervision of clinical staff using the provided soap by gently spreading soap lather over the entire lower legs and then rinsing them off thoroughly with lukewarm water. The skin was patted dry with a paper towel. After 15 minutes, patients were asked to complete a 10-cm VAS scale to rate their itch intensity and were evaluated for signs of erythema/redness and dryness by a dermatologist. Patients with a VAS score of 2.5–7.4 and a mild to moderate grade of erythema/redness as scored by the dermatologist evaluation continued in the study. Skicon measurements (for skin hydration), VapoMeter measurements (for TEWL), and MediCam digital imaging were performed, which served as baseline measurements. Subsequently, lotion was applied under the supervision of clinical staff, who also provided complete instructions to the subjects for at-home application. Following application of the test agent, patients remained in the environment chamber to complete a 10-cm

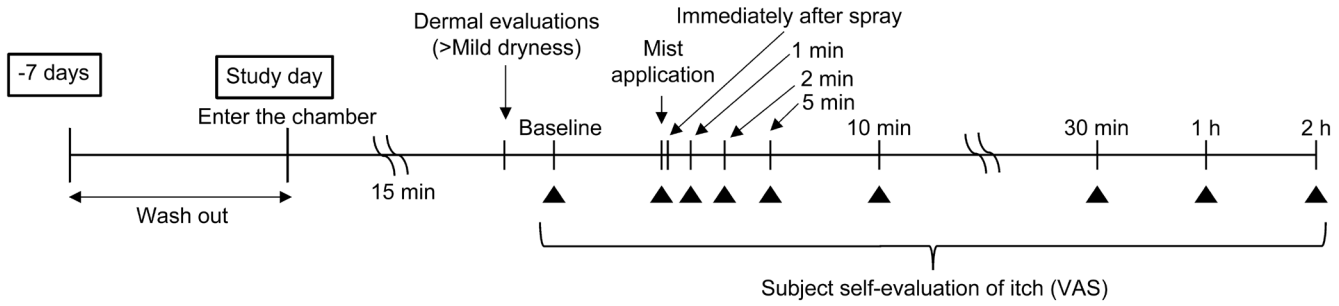

Figure 1. Procedure for evaluation of mist. The image demonstrates the research protocol. Black arrow shows the measure of self-evaluation of itching (VAS).

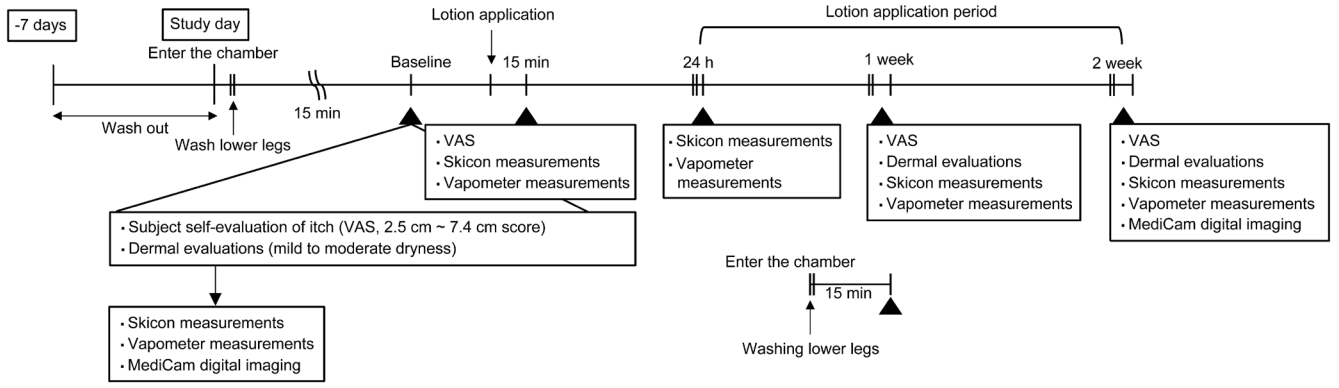

Figure 2. Procedure for evaluation of lotion. The image demonstrates the research protocol. Black arrow shows the measures of various evaluations depending on time points. Skicon and VapoMeter measurements were obtained at all time points. The self-evaluation of itching (VAS) was done at baseline, and after 15 minutes, week 1, and week 2 of application. We used the time interval of 15 minutes to evaluate amelioration after the first application and week 1 and week 2 to evaluate amelioration after continuous application. Dermal evaluations (erythema/redness and dryness) were conducted at baseline, week 1 and week 2 because amelioration in skin condition was expected with continuous usage. MediCam digital imaging was obtained at baseline and week 2 to compare results with the endpoint.

VAS scale regarding the intensity of their itch; VapoMeter and Skicon measurements were obtained as well. The subjects were instructed not to wash, wet, or rub the test sites for 24 hours. Subjects returned to the testing facility after 24 hours wearing loose apparel and removed long and tight boots prior to acclimation. VapoMeter and Skicon measurements were obtained after acclimating in the environment chamber having 20°C temperature and 50% RH for 15 minutes. The patients were instructed to apply the lotion twice-daily for a week prior to returning to the testing facility. They completed self-evaluation, dermatologist evaluation, and VapoMeter and Skicon measurements in the environment chamber after washing their entire lower legs as done initially. Subjects were again directed to apply the lotion twice-daily for 2 weeks prior to returning to the testing facility, and completed the entire procedure as done on first two occasions. Finally, subjects completed a consumer perception questionnaire.

Method of Applying Mist and Lotion

The mist was applied by CRL laboratory technicians. The mist was sprayed 6 inches away from the test site (more than one test site could be considered, but the site with maximum itching was evaluated) to ensure sufficient coverage by the applied liquid (1–2 pushes/test site, with 0.15 mL/1 push). The patients were instructed not to touch test sites during the period of evaluation (up to 2 hours).

The lotion was applied twice-daily , in the morning and the evening, preferably after the subjects had taken shower. The subjects applied two pumps (2 mL) of lotion manually on the entire lower leg and rubbed it until it was absorbed into the skin. Subjects were instructed to use the provided nonmoisturizing soap only for complete body washing and to refrain from using moisturizing products for the study duration.

Dermal Evaluations

The efficacy evaluation of the mist was conducted by a dermatologist by grading any observed dryness using the following scoring scale: 0 = none, ± = barely perceptible, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe.

For efficacy evaluation of the lotion, the selected lower leg was also evaluated by a dermatologist for signs of irritation, including erythema/redness and dryness. Any observed irritation was graded using the following 7-point grading scoring scale, considering half points: 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Subject's Self-evaluation of Itching

Subjects reported their itching sensation using a 10-cm VAS: 0 = not present to 10 = unbearable.

Hydration and Skin Barrier Properties

Skin hydration was measured as cutaneous conductance using SKICON-200EX (Yayoi Co. Ltd. Tokyo, Japan). Five Skicon readings were obtained from the selected lower leg, and mean value was calculated after excluding maximum and minimum values. Transepidermal water loss (TEWL) was measured using a VapoMeter (Delfin Technologies, Kuopio, Finland). Three VapoMeter measurements were obtained from the selected lower leg, and mean value was calculated. All measurements were obtained from the same area on each visit using a site locator.

Statistical Analysis

Changes in the study data were tested by Shapiro–Wilk test at a threshold of 1%. We used a paired *t*-test for normal data, and Wilcoxon signed-rank test was used for non-normal data, VAS score, hydration, and TEWL. The Wilcoxon signed-rank test was used for analyzing dermatologist's evaluations. All data were expressed as mean ± standard deviation (SD).

RESULTS

Efficacy Evaluation of Mist

In all, 35 subjects (7 men and 28 women, with an average age of 52.5 ± 11.2 years) used mist in the study. No adverse events were reported over the study duration.

Clinical evaluations of patients' itch scores with mild to moderate dryness on their arm, trunk, thigh, leg, posterior portion of the lower leg (calf), or shin demonstrated significant diminished skin conditions ($P < 0.001$) at all time points, compared to the baseline scores (Figure 3). Of all the subjects, 91.4% (32/35) who applied mist reported that their desire to scratch calmed down, 80% of the subjects (28/35) accepted that their skin felt moisturized, and 91.4% (32/35) indicated that their skin felt cooled (Figure 4).

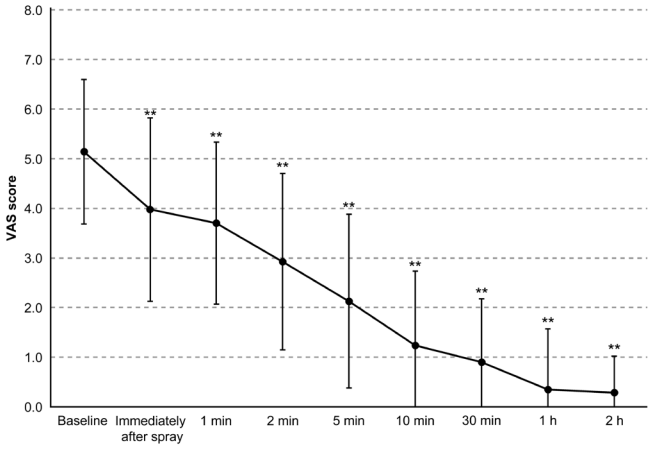

Figure 3. Changes in the self-evaluation of itching. The line graphs show VAS scores at baseline, 1, 2, 5, 10, 30 minutes, 1 hour, and 2 hours after the single application of mist. The Wilcoxon signed-rank test was performed to compare measurements immediately post-application versus the baseline score, at 1 minute post-application versus the baseline score, and at 2 minutes post-application versus the baseline score. The paired *t*-test was performed to compare measurements at 5 minutes post-application versus the baseline score, 10 minutes post-application versus the baseline score, 30 minutes post-application versus the baseline score, 1 hour post-application versus the baseline score, and 2 hours post-application versus the baseline score. Data are expressed as mean ± SD; $^{**}P < 0.001$.

Efficacy Evaluation of Lotion

In all, 34 subjects (2 men and 32 women, with an average age of 49.6 ± 8.1 years) completed the study with lotion. One subject withdrew for personal reasons. No adverse events were reported over the study duration.

Clinical evaluations of patients' itch scores who had mild to moderate dryness on the lower legs demonstrated significant improvement ($P < 0.001$) at all time points, compared to the baseline scores (Figure 5). Skin hydration increased significantly ($P < 0.001$) at all time points, compared to the baseline scores (Figure 6A). A significant decrease in itching ($P < 0.001$) was discovered in TEWL measurements at 15 minutes after applying the lotion; however, no significant decrease was observed at week 1 or week 2, compared to the baseline scores (Figure 6B). Clinical scores of erythema/redness and dryness diminished significantly

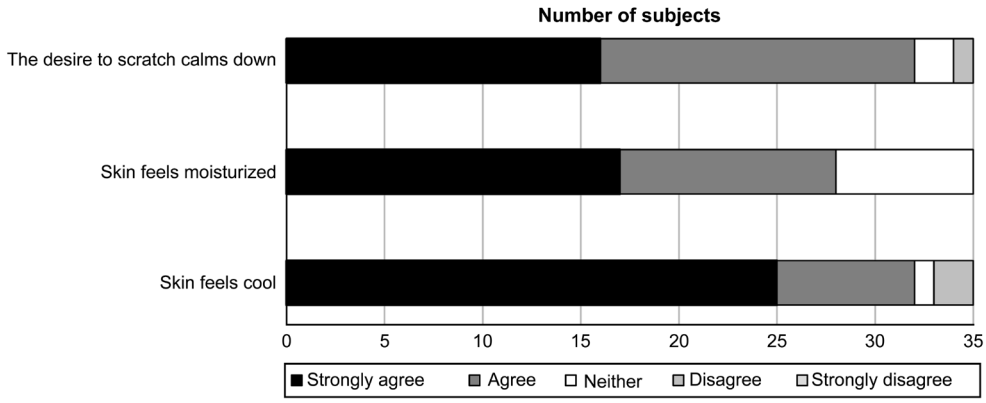

Figure 4. Consumer perception questionnaire. Diminished skin condition was observed after the single application of mist.

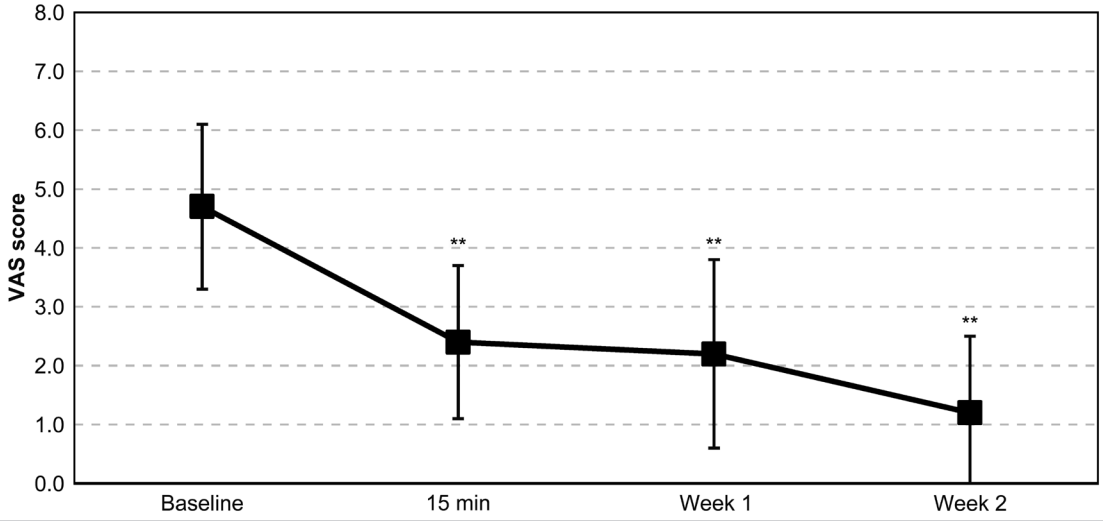

Figure 5. Changes in the self-evaluation of itching. The line graphs show VAS scores at baseline, 15 minutes, week 1, and week 2 after continuous use of lotion. Data are expressed as mean ± SD, and paired *t*-test versus the baseline score, $^{**}P < 0.001$.

at week 1 and week 2, compared to the baseline scores (Figures 7A and 7B). Figure 8 shows clinical diminishing of skin conditions and appearance. Desquamation and redness on the lower leg were observed at baseline; however, the picture indicates obvious diminishing of desquamation and redness after the continuous use of lotion. Of all the subjects, 97.1% (33/34) who had applied the lotion observed that their skin felt less itchy than before, 97.1% (33/34) accepted that the appearance of their skin improved, compared to prior manifestation, and 91.2% (31/34) observed that their skin felt moisturized (Figure 9).

DISCUSSION

Sensitive skin is a condition of subjective cutaneous hyperreactivity to environmental factors. Subjects who experience this condition report exaggerated reactions when their skin comes into contact with cosmetics, soaps, and sunscreens, and they often report worsening after exposure to dry and cold climate.[11] Sensitive skin is known to be less hydrated and more erythematous,[5] a disruption of the epidermal barrier function, resulting in constant perception of skin discomfort, such as itching, burning, stinging, and a tight sensation.[11] In particular, increased itching induces continuous scratching that destroys the skin barrier, thus forming a itch–scratch cycle that results in barrier disruption, resulting in chronic itching. In addition, because the quality of life is lowered in patients who suffer from itching, improvement in the quality of sensitive skin and abating of itching associated with it are required.[8–10]

As pathways of skin itching, the following two subtypes of itch-sensitive neurons, which are entirely separate and independent, are reported: histaminergic neurons and nonhistaminergic

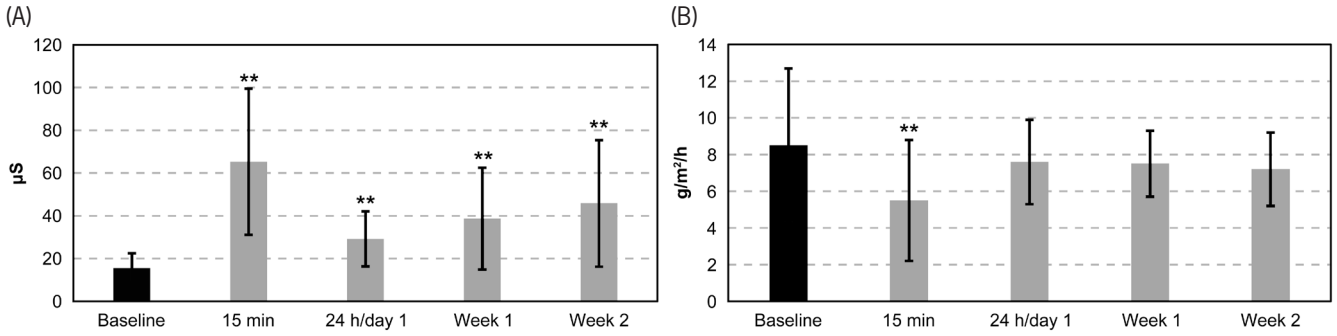

Figure 6. Changes in skin parameters. The bar graphs show (A) hydration, and (B) transepidermal water loss (TEWL) at baseline, after 15 minutes, 24 hours, week 1, and week 2 of continuous use of lotion. (A) Hydration: the paired *t*-test was used to compare measurements at approximately 15 minutes post-application versus the baseline score and approximately 24 hours post-application/day 1 versus the baseline score. The Wilcoxon signed-rank test was used to compare measurements at week 1 versus the baseline score and week 2 versus the baseline score. (B) TEWL: The Wilcoxon signed-rank test was performed to compare measurements at approximately 15 minutes post-application versus the baseline score, approximately 24 hours post-application/day 1 versus the baseline score, week 1 versus the baseline score, and week 2 versus the baseline score. Data are expressed as mean ± SD; $^{**}P < 0.001$.

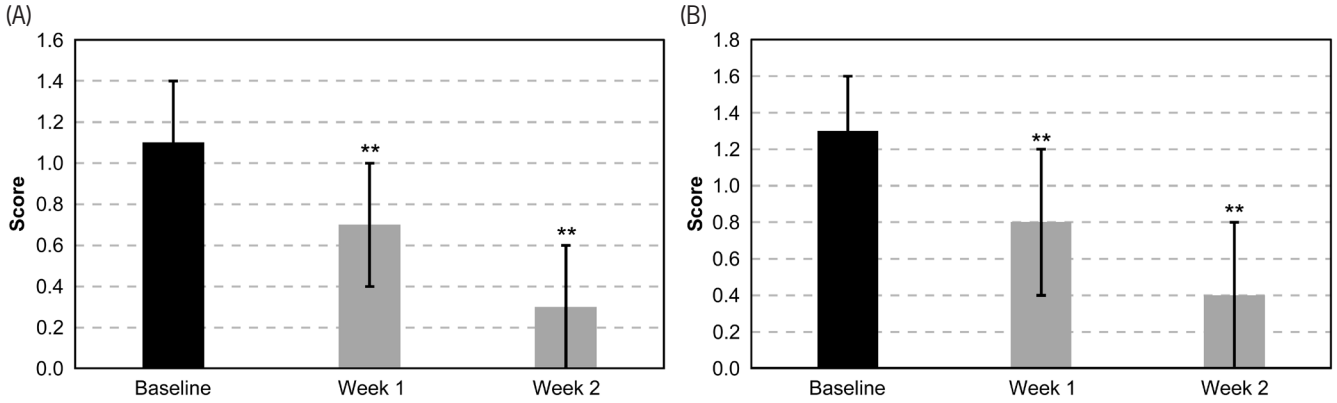

Figure 7. Changes in the evaluations of a dermatologist. The bar graphs show (A) erythema/redness, and (B) dryness at baseline after week 1 and week 2 after continuous application of lotion. Data are expressed as mean ± SD; Wilcoxon signed-rank test versus the baseline score, $^{**}P < 0.001$.

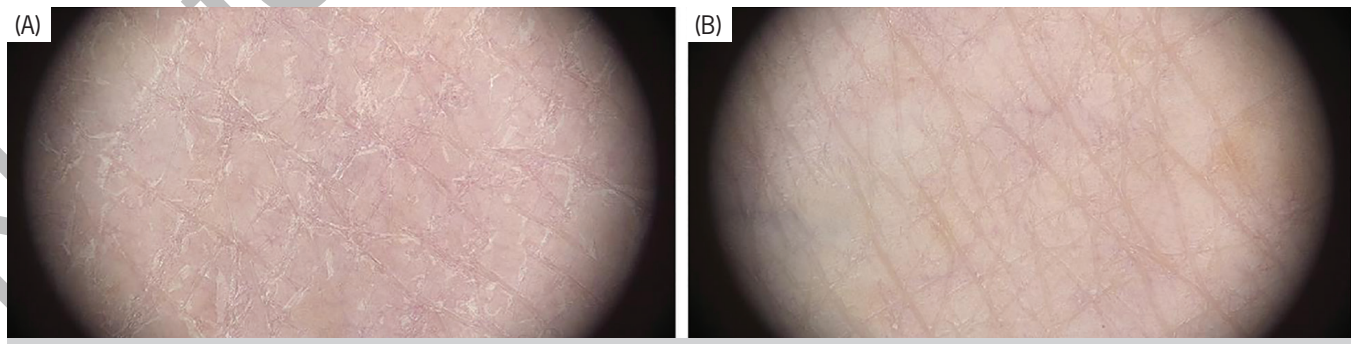

Figure 8. Skin appearance assessed by FotoFinder Medicam 1000. Typical clinical features on the leg of a subject at (A) baseline, and (B) week 2. At baseline, desquamation of the stratum corneum and redness were observed; however, they diminished at week 2 of treatment.

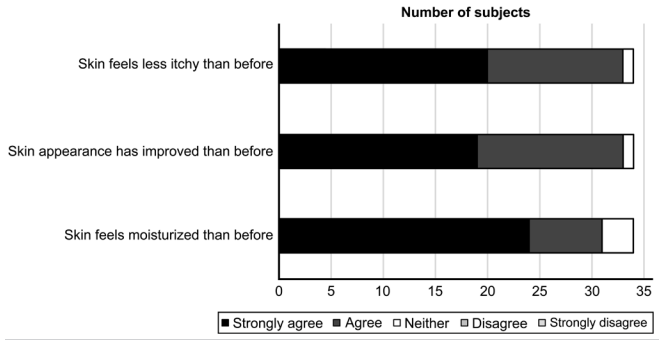

Figure 9. Consumer perception questionnaire. Diminished skin conditions were observed after using lotion for 2 weeks.

neurons.[12] Histamines are primarily released from mast cells, although other immune cells, including basophils and keratinocytes, also release histamines. H1 and H4 receptors on histaminergic nerves bind histamines and activate the transient receptor potential vanilloid type 1 (TRPV1) through the phospholipase system,[12] and the signals are transmitted to the brain. Histamines are primarily involved in acute itching (e.g., itch in patients with acute urticaria); hence, antihistamines targeting H1 receptors do not diminish chronic itching.[12] Chronic itching is induced by nonhistaminergic pathway, which is a relatively recent discovery.[6] Nonhistaminergic neurons can be elicited by endogenous/exogeneous pruritogens other than histamines (e.g., proteases, cytokines/chemokines, and amines) and express various receptors.[12] Interaction between substance P and NK1R is considered to be an important pathway of chronic itching. NK1R antagonists have been developed to treat chronic and refractory itching resulting from skin diseases, such as AD,[18] with reported amelioration.[21,22]

Nerve fiber reaction is involved in the hyperreactivity of sensitive skin which is considered to increase at reaction sites, such as nerve fiber elongation[23] and penetrating tight junctions.[24] A correlation is discovered between levels of NK1R expression and intensity of itching;[25] hence, any increase in the expression level of NK1R is also considered to cause itching.[26] In addition, because an increase in substance P-positive nerve fibers has been confirmed in patients with pruritic psoriasis,[27] inhibition of the interaction between substance P and NK1R is thought to relieve itching.[18]

In this study, we evaluated the effectiveness of two types of itch-relief moisturizers, mist and lotion, containing MTO, for people with self-perceived sensitive and dry skin, and those having itching because of dryness. MTO is an oligosaccharide comprising four α-D-glucopyranosyl units polymerized through α-1,4 glycosidic linkages, and is found to inhibit the activation of NK1R. As a result, both mist and lotion were effective in improving the itch score, indicating that the two types of moisturizers effectively relieved itching. We believe that the main benefit of spraying mist is its easy usability. Itching is thought to be induced by environmental changes, leading to dry skin;[28] therefore, mist was developed for quick relief from itching at patient's discernment. The mist spray effectively improved the itch score, with its effectiveness lasting for 2 hours. Menthol, a well-known cooling agent, was added in the mist spray to provide cooling effect to the skin.[29]

Lotion was developed to diminish the itching conditions associated with sensitive skin, such as dryness and redness, and to relieve itch by improving barrier function with its continuous use. We found that a twice-daily application of lotion containing MTO was effective for improving skin hydration, dryness, and redness measurements. This also ameliorated appearance of the skin.

It was accepted that improvement to the barrier function relieved skin itching; however, no significant change was observed in the TEWL value following a 2-week application of lotion, although there was a tendency toward a decreased value. This finding could be related to the renewal of skin cell roll over, which takes about 4 weeks; however, for feasibility and to minimize external factors, the endpoint of the effect of lotion was 2 weeks. We think this was one of the limitations in the designing of lotion and its use. Another limitation of the study design involving both mist and lotion was that we did not include a comparison without MTO; also, we did not include any other moisturizer for comparison. In order to demonstrate the function of MTO in itch-relief effect, we need to compare the effect of agents containing MTO with those without MTO. In addition, a comparison with other moisturizers is required. For example, moisturizers containing anti-itch additives, such as oatmeal and ceramides,[18] which are prescribed for mild to moderate itch, must be compared to a moisturizer containing MTO to confirm effectiveness of the current treatment.

CONCLUSIONS

In this study, we proved that two types of itch-relief moisturizers containing MTO are effective for individuals with self-perceived sensitive and dry skin, and having itching caused by dryness.

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FINANCIAL DISCLOSURE

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DECLARATIONS OF INTEREST

EriIchikawa, Akinori Inoue, Kenichi Matsuzaki, Sumi Kaneda, and Atsushi Naito are employees of Lion Corporation. Mihoko Yokoyama is a consultant for Lion Corporation.

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ORIGINAL CONTRIBUTION

The Immunomodulatory Power of Dupilumab: Implications for Keloid Scar Treatment

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ABSTRACT

Keloids are pathologic responses to cutaneous injury. Current treatments, such as topical and intralesional steroids and even surgical excision, have limited efficacy, creating a demand for improved therapies. Our study explores the functioning of dupilumab, an interleukin-4 and interleukin-13 signaling pathway inhibitor, in this context. We have reviewed the literature for using dupilumab to treat keloids, evaluating safety and efficacy and offering recommendations for its application. We searched PubMed and Google Scholar using "Dupilumab" and "Keloid" as keywords. To ensure relevance, we limited the search to English language publications of 2018–2023. Dupilumab exhibited efficacy in keloid treatment, with notable improvements in patients. One patient reported a 50% reduction in the fibrotic plaque and complete resolution of smaller keloids without adverse effects. Two other patients reported successful stabilization and reduction in keloids following dupilumab therapy; however, the 12-week treatment demonstrated no response or reduction in post-treatment size or height of keloidals, with disease progression observed in one patient. One report discouraged the use of dupilumab for keloids due to limited positive responses. Considering dupilumab as the last therapeutic option to treat keloids may benef patients resistant to standard therapies and/or those highly motivated to reduce keloids. (*SKINmed*. 2024;22:197–202)

Keloids are benign growths of a pathologic response to cutaneous injury resulting from an altered wound-healing process characterized by excessive production of collagen. They disproportionately affect the skin of colored patients, particularly the African American and Asian populations.[1,2] Keloids can be cosmetically disfiguring and symptomatically distressing, commonly causing pruritus and pain, and affecting the quality of life.[3]

Keloids exhibit a high propensity for recurrence, and the existing treatments, such as intralesional steroids, intralesional 5-fluorouracil, bleomycin, and surgical excision, have limited efficacy.[4] Consequently, there is a demand for improved therapies to address this unmet medical need. Novel approaches were sought, and one group recently highlighted the potential of dupilumab in treating keloids. This breakthrough was observed in a 53-year-old African-American man who had received dupilumab therapy for atopic dermatitis (AD).[5]

Dupilumab is a human monoclonal immunoglobulin G4 (IgG4) antibody that inhibits interleukin-4 (IL-4) and IL-13 signaling pathways by binding to the interleukin-4 receptor alpha (IL-4Rα) subunit, consequently altering cellular transcription.[6] Using real-time polymerase chain reaction (RT-PCR), a group of authors discovered the overexpression of genes associated with helper T cell type 2 (Th2), particularly IL-4 receptor and IL-13, in keloid tissue.[5] Inhibition of IL-4 and IL-13 signaling pathways by dupilumab reduces the proinflammatory and fibrotic processes contributing to keloids formation, thus helping to control and lessen the condition. Dupilumab's ability to modulate these immune responses makes it a potentially desirable treatment option for keloids, especially those unresponsive to conventional therapies.

Although more patients with keloids treated with dupilumab are documented, its exact role in treating keloids remains controversial and unclear.[7,8] Our paper intends to review the literature on keloids treated with dupilumab to assess its safety and efficacy,

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weigh the benefits versus risks for its use, and provide general recommendations for its use in this context.

METHODS

Our search was performed on PubMed and Google Scholar using the keywords "Dupilumab" AND "Keloid." The initial search on PubMed yielded eight papers, reflecting the niche disposition of this topic. To expand our scope, we conducted another search on Google Scholar using the mentioned keywords, which yielded 223 papers. To ensure the inclusion of the most recent and relevant studies, we restricted the Google Scholar search to English language papers published between 2018 and 2023. Additional inclusion criteria were established to select papers directly pertaining to dupilumab in treating keloids or its potential impact on development of keloids. We also considered reports cited within the selected studies from our search if they were deemed relevant to our paper's focus. Exclusion criteria were applied to all papers that did not meet the inclusion criteria.

DUPILUMAB FOR KELOID SCAR TREATMENT

Efficacy of Dupilumab

The first successful lessening of keloids with dupilumab treatment was reported in a 53-year-old African-American man who presented with severe AD, postinflammatory hypopigmentation, and two distinct nodules that had persisted for more than 2 years.[5] These included a prominent exophytic nodule (~5.5 × 5 cm) with raised borders and a smaller nodule situated adjacent to it in the right popliteal fossa. The nodules were surrounded by a substantial indurated region lacking standard skin lines and clinically and histologically confirmed as keloids. Prior to initiating dupilumab treatment, the patient had received more than six intralesional triamcinolone injections with minimal improvement. The patient regimen of 300-mg dupilumab subcutaneous injections for severe Aseven in 2018, administered every two weeks. Significant lessening in AD and keloid was observed 7 months after the dupilumab treatment. This was reflected by a 50% reduction in fibrotic plaque, accompanied by shrinkage of the larger keloid, flattening of its surrounding borders, and complete disappearance of the smaller keloid. Importantly, regular skin lines were visible after the treatment without any reported adverse effects.[5]

A 37-year-old South Asian woman presented with a tender and inflamed keloid on the sternum from a past ruptured cyst.[9] Although topical anesthetics, cooling methods, and vibratory distractions were used, the patient could not tolerate intralesional steroids. The patient received a 600-mg dupilumab subcutaneous injection and 300 mg every 2 weeks. No change in the size of keloid but a noticeable reduction in pain was observed at the 4-week follow-up. The patient continued dupilumab therapy for 3 months, resulting in a near complete absence of her manifestations, although size of the keloid remained unchanged. No adverse effects were reported. The patient was able to wear clothing comfortably without any restrictions. Satisfied with the outcome, she declined additional treatment, including continuation of dupilumab. About 4 weeks after her last injection, the patient experienced a gradual return of itching and pain associated with her keloid; however, she didn't return for follow-up.[9]

In a case series conducted by a group of researchers, dupilumab was used adjunctively to stabilize regrowth of keloid after surgery and radiation for severe and chronic keloids.[10] A 23-year-old woman presented with extensive and painful keloids covering her upper shoulders and the chest from truncal acne. Her keloids were unsuccessfully managed for 10 years with intralesional triamcinolone injections. She was subsequently treated with bilateral surgical excision, followed by skin grafting and three fractions of 18-Gray (Gy) radiation. A year later, although her left side remained quiescent, her right side became tender and elevated, which was treated with additional series of intralesional triamcinolone injections with no resolution in manifestations. Because her right shoulder remained inflamed, the patient was initiated 600-mg dupilumab subcutaneous injections, followed by 300-mg dupilumab every 2 weeks. Within a month, her pain, pruritus, and inflammation lessened. Following 3 months of stabilization, intralesional therapy was reintroduced, leading to a successful reduction in the size of her keloids. Her right side keloid remained quiescent for 8 months, and she continued with dupilumab therapy without any adverse effects.[10]

Another patient, a 20-year-old woman, reported with keloids, measuring 0.5–1.5 cm, on her chest, back, and shoulders.[10] She declined isotretinoin but partially responded to oral tetracycline family of antibiotics. Intermittent eruptions led to the formation of more keloids, with limited response to intralesional corticosteroids. The patient was initiated 600-mg dupilumab subcutaneous injection, followed by 300-mg dupilumab every 2 weeks. The patient did not develop additional keloids despite new acne eruptions. The patient, 2 months into the treatment, reported reduced pruritus and discomfort, and her skin lesions were less elevated and erythematous. At the 5-month follow-up, she exhibited continuous recovery with ongoing dupilumab treatment without any reported adverse effects.[10]

Nonresponsive to Dupilumab

A study was conducted with two 17-year-old patients with widespread keloids, both with a strong family history of keloids. Both were treated with 300-mg dupilumab every 2 weeks for 12 weeks.[11]

Concurrently, one keloid was selected in each patient for a single subepidermal injection of 0.1-cc dupilumab.[11]

Patient 1 was a Middle Eastern woman with a 7-year history of expanding keloids on her chest and back, occurring close to uncontrolled acne in the same areas. Approximately 4% of her body surface area (BSA) was affected. No improvement in her keloids was observed with intralesional corticosteroid bimonthly therapy for 3 years. New keloids appeared in spite of achieving control of her acne through a regimen of topical clindamycin, benzoyl peroxide, tretinoin, and oral doxycycline.[11]

Patient 2 was an African-American man with 1-year history of rapidly expanding diffused keloids on the jaw, upper back, and upper chest, all related to deficiently managed folliculitis and pseudofolliculitis barbae.[11] Approximately 3% of his BSA was affected. The past interventions included surgical removal of a lesion on the mandible, followed by post-surgical intralesional corticosteroid injections that prevented recurrence and a 2-month isotretinoin regimen that failed to halt the progression of both folliculitis and keloids.

Both patients observed no decrease in the size or height of keloids with dupilumab therapy; this was verified through comparative clinical photography. Patient 1 indicated disease progression, with enlargement of some existing lesions and development of new lesions. She also reported no relief from pruritus or pain associated with keloids. Patient 2, however, indicated no disease progression, and his lesions remained symptom-free. Both patients discontinued dupilumab therapy after 3 months; however, patient 1 started pulsed dye laser and CO_2 laser treatment combined with corticosteroid therapy.[11]

In a study, six men and two women of various ethnicities were treated with dupilumab therapy.[8] The mean age of the patients was 33.75 years (range 23–52 years). The treatment response for keloids was evaluated through clinical assessment by one of the authors or by self-assessment performed by patients. Patients received 300-mg dupilumab subcutaneously every 2 weeks for a minimum of 2 months and maximum of 1 year. Of the eight patients, only one observed a possible, although questionable, response and chose to continue with the treatment. Four patients demonstrated no improvement, and three observed disease progression. Of the patients who experienced aggravation, one had significant development of the disease. All patients were recommended to discontinue dupilumab treatment. The authors concluded that the findings did not support dupilumab therapy and advised against its off-label application for treating keloids.[8]

A concise overview of the case reports assessed in this review is given in Table 1.

DISCUSSION

The patients reviewed in our paper demonstrated variable patient responses to intralesional dupilumab injections for treating keloids, reflecting the inconsistent effectiveness of this regimen. While some patients experienced significant decrease in keloids and associated manifestations, such as pain and pruritus, others observed no change in manifestations with dupilumab therapy. No clear pattern was observed for identifying patients benefited with dupilumab therapy in addition to the absence of specific factors contributing to nonresponsive perception, thus highlighting the complexity of managing this condition.

A consistent finding across all studies was that adverse effects were either reported as absent or not reported. While this could be compelling, it highlighted a limitation in data collection. The consistent absence of adverse effects indicated a reporting bias, as studies not reporting adverse events are more likely to be published. One case report documented a patient on dupilumab treatment for more than 11 months, suggesting a favorable long-term safety profile;[10] however, this was observed in a single study within our search. Additional long-term investigations are required to provide a better assessment of dupilumab's safety and efficacy. In this context, the limited availability of information on the potential adverse events restricted the complete understanding of dupilumab's safety profile.

It is crucial to weigh the financial implications of biologics and the potential for adverse events, mainly when dupilumab is prescribed solely for symptomatic relief from keloids.[9] This requires comprehensive patient education and thorough assessment of factors related to patient, such as treatment goals, past medical history, immunosuppression status, etc. because shared decision-making between the physician and patient makes for well-informed decisions regarding treatment regimen.[9]

CONCLUSIONS

Considering dupilumab as a last line of therapeutic option to treat keloids may benefit patients who have not responded to standard therapies or express a strong desire to alleviate clinical manifestations because dupilumab has the potential to enhance the quality of life. Because of the inconsistent results identified in this paper, physicians should prescribe dupilumab on a case-by-case basis, tailoring to each patient's specific needs and vigilantly monitoring for therapeutic and adverse effects. The future research must investigate the determinants of dupilumab efficacy and refine its application in keloid treatment protocols.

Table 1. Summary of Important Case Report Findings of Dupilumab Use for Keloid Treatment

Author	Patient age/ gender	Ethnicity	Prior treatments	Dosage Series	Treatment Response	Follow-up
Diaz et al.[5]	53/M	African American	Intralesional triamcinolone injections	300-mg sub-Q subcutaneous every 2 weeks Total duration not specified	• ~50% reduction in fibrotic plaque, shrinkage of the larger keloid, flattening of its surrounding borders, and complete disappearance of smaller keloid	7 months
Wong et al.[9]	37/F	Asian	N/A	600- mg sub-Q subcutaneous, followed by 300 mg every 2 weeks for 3 months	• Near absence of her manifestations • Overall size of the keloid unchanged	3 months
Wittmer et al.[10]	23/F	White	Intralesional triamcinolone injections, surgical excision, radiation	600-mg sub-Q subcutaneous, followed by 300 mg every 2 weeks for 11+ months	• Pain, pruritus, and inflammation subsided • Reduction in size upon reintroduction of intralesional therapy	11+ months
	20/F	White	Oral tetracycline	600-mg sub-Q subcutaneous, followed by 300 mg every 2 weeks for 5+ months	• No additional keloids developed • Reduced pruritus and discomfort, and lesions appear less raised and erythematous	5+ months
Luk et al.[11]	17/F	White	Intralesional corticosteroid therapy, oral doxycycline	300-mg sub-Q subcutaneous every 2 weeks for 12 weeks	• No reduction in keloid size or height • Progression of some existing lesions • Development of new lesions • No improvement in pruritus or pain	N/A
	17/M	African American	Intralesional corticosteroid therapy, isotretinoin	300-mg sub-Q subcutaneous every 2 weeks for 3 months	• No response • Lesions remained symptom-free	N/A

Guttman-Yassky et al.[7]	30/F	African American	N/A	300-mg sub-Q subcutaneous every 2 weeks for 12 months	• No response	N/A
	25/M	Asian	N/A	300-mg sub-Q subcutaneous every 2 weeks for 12 months	• Disease progression	N/A
	52/M	African-American	N/A	300-mg sub-Q subcutaneous every 2 weeks for 2 months	• Lack of response	N/A
	27/M	†Indian	N/A	300-mg sub-Q subcutaneous every 2 weeks for 2 months	• No response	N/A
	39/M	Caucasian	N/A	300-mg sub-Q subcutaneous every 2 weeks for 6 months	• No response	N/A
	39/M	African American	N/A	300-mg sub-Q subcutaneous every 2 weeks for 12 months	• Questionable response	N/A
	35/F	Caucasian	N/A	300-mg sub-Q subcutaneous every 2 weeks for 3 months	• Disease progression	N/A
	23/M	Caucasian	N/A	300-mg sub-Q subcutaneous every 2 weeks for 10 months	• Disease progression	N/A

†Unsure of what this means as the study did not specify American Indian versus Asian Indian.

CONFLICTS OF INTEREST

The authors had no financial or nonfinancial conflict of interest to disclose. All authors were granted permission from the copyright holder for tables, figures, images, and illustrations used in the manuscript.

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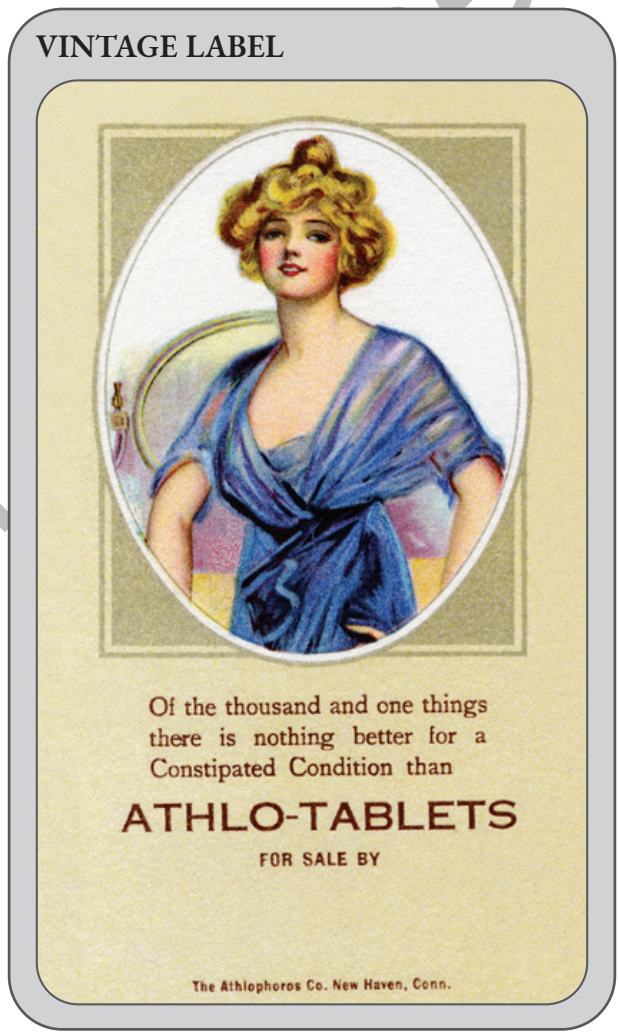
VINTAGE LABEL



ORIGINAL CONTRIBUTION

Women in Dermatology: Considerations over Their Recognition and Prominence

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ABSTRACT

According to the Federal Council of Medicine's demographic data from 2020, the medical specialty with the highest number of women is dermatology; with 77.9% within the total of 9,078 specialists. The male/female ratio is 0.28, that is, for each man, there are more than 3 women Dermatologists. Analyze the participation of women in Brazilian dermatology and their representation in leadership positions through data review. A literature review of the National Library of Medicine PubMed database was performed in May 2022 and data review of the SBD database. According to the Brazilian Society of Dermatology (SBD), about 80% of its associated Doctors are women. Despite this correlation, since its foundation in 1912, the SBD has already had 62 directorates, of which 53 were known to be presided over by men and 4 of them are unknown. Among the directorates that are known, only five (8.62%) were chaired by women.. (*SKINmed*. 2024;22:203–204)

In the history of medicine, since the institutionalization of medical education in the Middle Ages, only men were privileged to partake it.[1] Women who were interested in and dedicated to medical practice were often condemned and penalized as practitioners of witchcraft.[1] The first woman to challenge this system, Margaret Bulkley, disguised herself as a man so that she could be accepted into the medical school, thus evolving into the notable case of renowned British Armed Forces surgeon Dr. James Barry (1799–1865).[1]

The first medical school for women, the "Female Medical College of Pennsylvania," was established in 1850; however, in Brazil, Dom Pedro II allowed women to pursue a medical career only in 1879.[1] Further, many women were forced to give up maternity or marriage to dedicate themselves to medical practice for the sake of ostensibly equal opportunities in such an imbalanced environment.

Among medical specialties, dermatology is the area of interest among women. In 2011, the Women's Dermatologic Society (WDS) consisted of 865 women as its members in North America, compared to 100 men dermatologists.[2] In addition, according to the Conselho Federal de Medicina (Brazilian Federal Council of Medicine), in 2020, dermatology had the highest number of women specialists, constituting 77.9% of the total 9,078 specialists.[3] The man–woman ratio in dermatology is 0.28, that is, for each man, there are more than three women dermatologists.[3] In spite of a higher number of women specializing in dermatology in Brazil and worldwide, it is unclear why only a small proportion is appointed to higher academic or leadership and decision-making positions.[3]

In this report, the authors analyzed the participation of women in the fileld of Brazilian dermatology, their representation at leadership positions, and the reasons and results of this analysis.

According to the Sociedade Brasileira de Dermatologia (SBD; Brazilian Society of Dermatology), approximately 80% of its associated members are women. Yet, since its foundation in 1912, the SBD has had 62 directorates, 53 of which were presided over by men and four of them were the gender of the chair. Among the directorates that are known, only five (8.62%) were chaired by women.[4] The first woman to become president of the SBD was Professor Sarita Maria de Fátima Martins de Carvalho Bezerra, who took office in 1996, more than 84 years of establishing of this society.[4] The other four women dermatologists who presided over

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this society were Clarisse Zaitz in 1998, Alice de Oliveira de Avelar Alchorne, 2007–2008, Bogdana Victoria Kadunc, 2011–2012, and Denise Steiner, 2013–2014.

Considering these findings, it is surprising to observe a disproportional representation of women and a few women dermatologists at leadership positions in Brazilian society. Gender inequality in the professional sphere remains a significant social problem in Brazil that has extended beyond the medical field. Lack of women expressiveness in the management of institutions significantly exposes this social gap. The data released by the Brazilian Institute of Geography and Statistics (IBGE) in 2019 revealed that only 37.39% of higher positions are occupied by women.

Considering these data, a strong cultural issue is involved in the access of women to higher positions in these entities. This deterrent initially was attributed to a strong antifeminist historic context, built on a patriarchal basis, that has perpetuated in organizational models, in addition to a lack of inspiration and examples of successful women at prominent positions.[6] In addition, the majority of women assume multiple household tasks, dividing their time and dedication, which negatively interferes with professional opportunities.[7] Finally, the failure to recognize the importance of women is reflected by the low number of programs that encourage women as candidates for higher positions.

The Brazilian society in which the majority of its members are women but the majority of its leaders are men appears incongruous, necessitating a change in its current and future structure; however, such a change could be possible through daily recognition of inequalities. The task is lengthy and the effort is intense until the fruits of feminine representation are harvested, but newer generations must understand the importance of building a different story from the one being written.

In this sense, the role of SBD as a great motivator for the effective participation of women specialists in the society becomes important. Women must be encouraged to be protagonists, and it is up to the feminine dermatologic community to dedicate itself to becoming the identity of this specialty. Such an effective representation could be achieved through scientific development, academic participation, and leadership in medical societies. It takes a desire for a change to have our space respected and represented.

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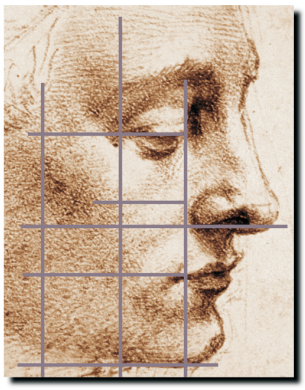

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COOPER CASES AND COMMENT
Warren R. Heymann, MD, Section Editor

The Mystery of an Inflamed "Soul Patch"

Kayla Brockmeyer, BS;[1] Patrick McMahon, MD[2]

A 20-year-old man had developed dermatitis on his scalp and facial hair between his lower lip and chin, his 'soul patch', for one month. He initially presented to urgent care, where the dermatitis was attributed to *Herpes simplex* infection, for which he was treated with both oral valacyclovir and topical acyclovir. When no change was observed, he consulted his pediatrician, who prescribed oral clindamycin and referred him to dermatology. Physical examination revealed a crusted plaque on an erythematous and edematous base at the lower cutaneous border of the lower lip (Figure 1). Examination additionally revealed an erythematous scaling plaque on the left temporal area with associated flaking, tenderness, and hair loss and left-sided cervical lymphadenopathy. A fungal culture grew *Trichophyton mentagrophytes*, but a bacterial culture did not grow. Further investigation revealed that he had a dog; however, no other animal contact to account for a fungal reservoir was present. He was successfully treated with oral terbinafine for 6 weeks, plus ketoconazole 2% shampoo and ketoconazole 2% cream with complete resolution (Figure 2). (*SKINmed*. 2024;22:206–207)

DISCUSSION

Tinea capitis and tinea barbae fungal infections are relatively uncommon in the adult population. In the United States, tinea capitis is often attributed to the anthropophilic fungi *Trichophyton tonsurans*.[1,2] Causative agents of tinea barbae include both zoophilic and anthropophilic fungi, with more recently reported patients being infected with *Trichophyton tonsurans* and *Trichophyton rubrum* worldwide.[2–6]

In the United States, tinea capitis is normally caused by *Trichophyton tonsurans*.[1,2] It is usually noninflammatory but with associated scaling and alopecia. *Trichophyton mentagrophytes* is a rare causal agent of tinea capitis in the United States, accounting for only 0.5% of patients.[1] The presentation is inflammatory with associated erythema, tenderness, pustular folliculitis, and lymphadenopathy. More severe infections may lead to the formation of kerion.[2] Tinea barbae, according to recent reports, suggests a rise in anthropophilic fungi as causal agents, compared to zoophilic fungi, specifically *Trichophyton rubrum* and *Trichophyton tonsurans*,[2–6] and is probably due to autoinoculation associated with onychomycosis, tinea pedis, or shaving.[3,6]

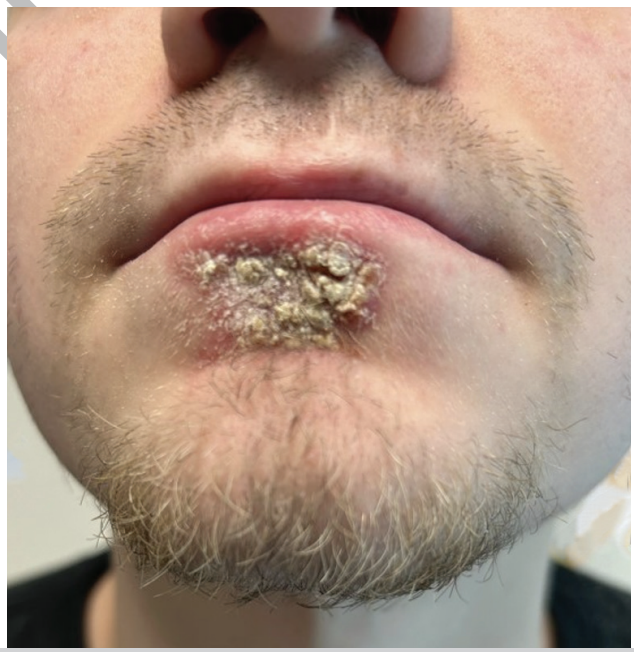

Figure 1. Crusted plaque with erythematous and edematous base involving the lower lip and labiomental groove.

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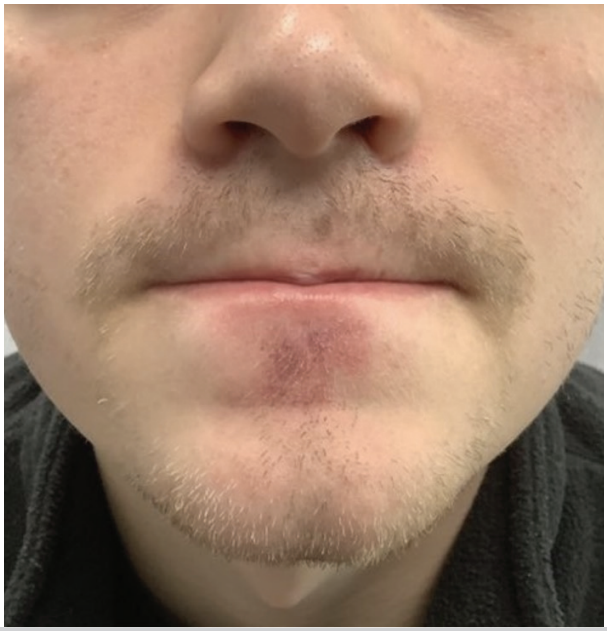

Figure 2. Resolution of clinical manifestations after 6 weeks of treatment with oral terbinafine.

Although anthropophilic infections often result in a superficial infection with scattered papules and pustules, *Trichophyton mentagrophytes* infection may create an inflammatory response with associated erythematous plaques, pustular folliculitis, and kerion formation.[2,5]

Presentation of our patient supports the rare occurrence of *Trichophyton mentagrophytes* as the causal agent for inflammatory tinea capitis and tinea barbae. Such an etiology is rare in developed countries, often mistaken for acne, bacterial folliculitis, or *Herpes simplex* infection.[2,4,5] A lack of treatment response with antimicrobials or antiviral agents, coupled with an inflammatory presentation, could indicate a dermatophyte infection.

This situation highlights the role of atypical fungal species as the underlying organism in dermatophyte infections, even in the United States. Should the response to oral terbinafine had been poor, infection by *Trichophyton indotineae* would have been suspected. *Trichophyton indotineae*, once thought to be a subtype of *Trichophyton mentagrophytes*, is now considered as a terbinafine-resistant species that has emerged from South Asia to the United States. *Trichophyton indotineae* infection creates a similar inflammatory presentation as *Trichophyton mentagrophytes*; however, it is often misidentified as *Trichophyton mentagrophytes* in routine mycology testing, ultimately requiring genomic sequencing for the diagnosis.[7] *Trichophyton indotineae* usually responds to oral itraconazole or griseofulvin.

While the current trends favor anthropophilic fungi as common causative agents of dermatophyte infections in the United States, we must still consider zoophilic and novel fungi in our daily practice.

CONCLUSIONS

In the United States, tinea capitis and tinea barbae are fungal infections typically caused by anthropophilic fungi. Zoophilic fungi, including *Trichophyton mentagrophytes*, may cause inflammatory tinea capitis and tinea barbae, lymphadenopathy, and kerion formation. If inflammatory tinea infections do not respond to oral terbinafine, then this must prompt a high clinical suspicion for *Trichophyton indotineae* infection.

PATIENT CONSENT

The authors obtained consent for the publication of recognizable patient photographs or other identifiable material.

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DERMATOLOGIC DIAMONDS

Sylvia Hsu, MD, Section Editor

Pediatric Herpes Zoster after Chickenpox Vaccination

Sean A. Na, MD; Jordan T. Hyde, MD; Sylvia Hsu, MD

DERMATOLOGIC DIAMONDS

- Even in the absence of the past varicella infection, herpes zoster (HZ) must be considered in pediatric populations inoculated with the live attenuated chickenpox vaccine.
- While pediatric therapies for herpes zoster include oral valacyclovir and intravenous acyclovir, the latter may be preferred to prevent morbidity and mortality associated with complicated HZ.
- Immunodeficiency must be investigated in pediatric patients presenting with HZ without a primary infection.

Herpes zoster (HZ) is a viral-mediated condition caused by the reactivation of varicella-zoster virus (VZV), also known as human herpes virus 3. HZ classically presents in older adults as an acute painful eruption of lesions on an edematous and erythematous base in a dermatomal distribution.

After the initial VZV infection, the virus remains dormant in the sensory ganglion of a cranial nerve or the dorsal root ganglion of a spinal nerve until reactivation due to a number of factors, such as stress, medication, illness, re-exposure, or malignancy. These factors are theorized to weaken the immune system, inducing viral replication, virion shedding, and retrograde axonal transport in the ganglion's dermatomal distribution. The resulting acute dermatomal eruption often comes with significant pain, burning, tingling, dysesthesia, and pruritus. Other less common manifestations include fever, headache, fatigue, and photophobia. Occasionally, severe manifestations may arise from HZ, such as herpes zoster oticus (Ramsay Hunt syndrome), herpes zoster ophthalmicus, acute retinal necrosis, disseminated zoster, aseptic meningitis, and post-herpetic neuralgia.

HZ is typically observed in patients with a history of primary varicella infection, also known as chickenpox. The incidence of primary varicella infection has decreased since 1995 due to the development of the live attenuated VZV vaccine. Rare reports of HZ in vaccinated pediatric patients without history of primary varicella infection are described in the literature.[1] As such, HZ must be considered in the examination of pediatric patients without prior varicella infection, as the live attenuated disposition of the varicella vaccine may cause a subclinical primary varicella infection or mutations of the live vaccine itself. The Centers for Disease Control (CDC) recommends a two-shot series given between 12–15 months and 4– 6 years.[2] Live vaccines, such as measles, mumps, rubella (MMR) or varicella, have the risk of reversion to virulence as wild-type or mutation to novel strains. This reversion may occur through mutations during viral replication or interference by related viruses.[3] Pediatric patients with a family history of immunodeficiencies, such as severe combined immunodeficiency (SCID), Wiskott–Aldrich syndrome, hyper-immunoglobulin M (IgM) syndrome, and X-linked agammaglobulinemia, should first be investigated with genetic screening panels prior to inoculation with live vaccines to prevent the incidence of such phenomena.

PATIENT

A 19-month-old healthy Hispanic girl presented with a 2-day history of pruritic eruptions overlying her right upper back (Figure 1). Her mother denied any significant dermatologic

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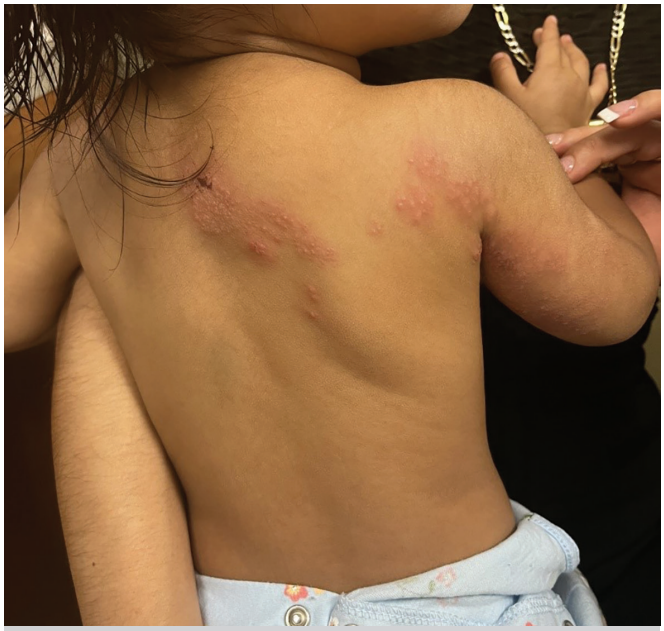

Figure 1. Dermatomal distribution of grouped lesions in a 19-month-old child.

history, including chickenpox, known allergies of the child, recent travel, recent illness, or sick contacts; similarly, a 14-point review of systems, including fevers, chills, irritability, feeding problems, or respiratory distress, was negative. At this visit, her mother stated that the child was up to date regarding her vaccinations, including the first two immunizations of the varicella vaccine received at the age of 12 months. A full skin examination revealed no abnormalities, except grouped lesions on an erythematous base in a dermatomal distribution overlying the patient's right upper back and extending to her right proximal posterior arm.

Consultation with the pediatric infectious disease service recommended intravenous acyclovir infusion whereas the pediatric dermatology consultant recommended oral acyclovir. Risks and benefits of both therapies were discussed, and the patient was transferred to the emergency department of a neighboring children's hospital for further evaluation and treatment for presentation\ consistent with HZ.

Oral acyclovir, 20 mg/kg/dose four times daily for 7–10 days was initiated. Additionally, human immunodeficiency virus (HIV) testing, lymphocyte CD4–CD8 count, and differential complete blood count (CBC) were normal. Subsequently, follow-up with pediatric immunology was scheduled 7 days after the initial presentation for an additional immunodeficiency diagnostic examination which was also negative.

TREATMENT

In adults, the literature is clear about uncomplicated HZ treatment. Antiviral therapy, especially within the first 72 hours, in the form of oral valacyclovir or famciclovir (first-line) or acyclovir (second-line), is recommended to decrease the severity and duration of clinical manifestations, reduce risks of transmission, encourage healing of existing lesions, and to prevent eruption of new lesions and post-herpetic neuralgia.[4,5] Additionally, patients with any immunologic disorder are recommended to begin antiviral therapy regardless of the time of onset of lesions.[6] Certain patients with complicated HZ, such as herpes zoster ophthalmicus, acute retinal necrosis, acute herpes zoster oticus, and symptomatic neurologic complications (meningitis, encephalitis, or myelitis), may necessitate intravenous antiviral therapy.[7]

The literature is not sufficient about the therapeutic approach to HZ in pediatric patients, probably because of its relative rarity, compared to HZ classical clinical onset in adults. While valacyclovir is approved by Food and Drug Administration (FDA) exclusively for children aged 2 years or older, studies have reported the occurrence of herpes zoster ophthalmicus and aseptic meningitis in pediatric populations, including neonates. As such, the possibility of complicated HZ within this population may necessitate the use of intravenous acyclovir over oral forms of antivirals, such as valacyclovir, especially considering the inability of neonates and infants to ingest tablets.[8,9]

CONCLUSIONS

Clinicians should recognize the rare but possible probability of HZ in young children without an apparent history of varicella infection, especially in children partially or completely inoculated with live vaccines, such as varicella or MMR.[10] While HZ is not encountered frequently and may not be high on the differential diagnosis list within the pediatric population, it still deserves consideration as a potential diagnosis in younger children presenting with vesicular eruptions overlying an erythematous and edematous base in a dermatomal distribution. Intravenous acyclovir may be preferred, especially in pediatric patients, to prevent the morbidity and mortality associated with complicated HZ. A thorough examination for an immunocompromised state must be considered on a case-by-case basis.

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Snejina Vassileva, MD, PhD, Section Editor

Subcutaneous Nodules of the Vulva

Anissa Zaouak, MD;[1] Ehsen Ben Brahim, MD;[2] Takoua Bacha, MD;[1] Olfa Midassi, MD;[1] Houda Hammami, MD;[1] Samy Fenniche, MD[1]

A 32-year-old patient complained of three slow-growing subcutaneous nodules on her right labius majus, present for 3 years. Her past medical history was unremarkable. Cutaneous examination revealed three subcutaneous nodules of 1 cm diameter firmly adherent to the underlying tissues, located on her right labium majorum (Figure 1). Regional lymph nodes were not enlarged. She underwent an excision biopsy of a subcutaneous nodule under local anesthesia. The gross specimen was firm, white and fleshy in appearance. A skin biopsy was performed, and histological findings revealed a non-encapsulated dermal nodule composed of clusters of polygonal cells with small central nuclei and abundant eosinophilic cytoplasm (Figure 2a). The tumor cells formed sheets and nests irregularly infiltrating between collagen bundles. There was no significant cytologic atypia and mitotic features. There were no necrosis and hemorrhage. The cells were positive for S-100 immunostain (Figure 2b). Hence, the diagnosis of benign vulvar granular cell tumor was assessed. The patient underwent surgical excision of the subcutaneous nodules with no recurrence at 2 years. (*SKINmed*. 2024;22:213–214)

DISCUSSION

Granular cell tumors are uncommon soft tissue neoplasms originating from the neural sheath.[1] They are usually located on the head and neck, especially on the tongue and oral cavity. Vulvar involvement, as in our patient case, has been reported in 7%–16% of cases.[2] The most common location of granular cell tumor in the female genital tract is on the labium majus.[1]

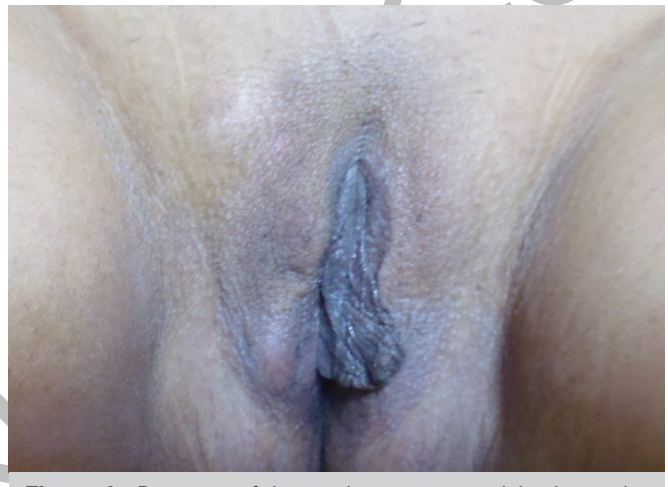

Figure 1. Presence of three subcutaneous nodules located on the right labium majus.

Clinically, they present as asymptomatic slow growing solitary subcutaneous nodules. In our patient case, the subcutaneous nodules were multiple. They are usually benign and occur more often in women.

Granular cell tumor was first reported by Abrikossoff in 1926.[3] The clinical differential diagnosis may include a sebaceous cyst, lipoma, fibroma, papilloma, hidradenoma, epidermal cyst, and Bartholin's cyst.[4,5] Histologically, granular cell tumor may be confused with the granular cell variants of basal cell carcinoma, melanoma, leiomyoma, leiomyosarcoma, dermatofibrosarcoma, angiosarcoma, and fibrous histiocytoma. Immunohistochemical stains are usually useful to distinguish subcutaneous nodule from the other tumors as it stains negative for desmin, cytokeratins, epithelial membrane antigen, and glial fibrillary acidic protein.[1] In about 1%–2%, granular cell tumor could be malignant and associated with regional and distant metastases recommending a long follow-up in these patients, especially to diagnose a local recurrence.[5] Treatment relies mainly on surgical excision with wide margins because the tumor has irregular margin.

CONCLUSIONS

Vulvar subcutaneous nodules may vary from benign to malignant tumors. Granular cell tumors are uncommon tumors that could be easily misdiagnosed, especially when they are located in

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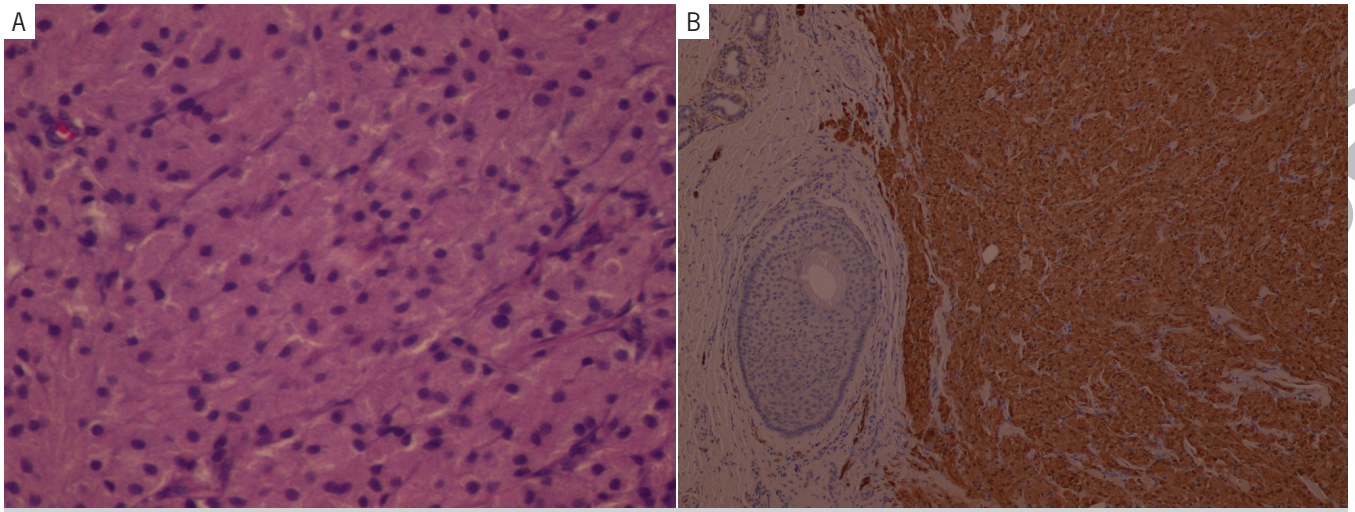

Figure 2. (A) Presence of clusters of cells with small central nuclei and abundant eosinophilic cytoplasm (HEX100). (B) The cells were positive for S-100 immunostain.

the vulva. A careful correlation of the clinical and histopathologic findings is important for a rapid and correct diagnosis.

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Triad of Thyroid Ophthalmopathy, Dermopathy, and Acropachy

Annie Jin, MD;[1] Medhavi Jogi, MD;[2] Sylvia Hsu, MD[1]

A 40-year-old African-American man was referred to our dermatology clinic for management of his long-standing thyroid dermopathy. The patient was diagnosed with hyperthyroidism at the age of 20, and was treated with radioactive iodine I-131 but subsequently lost to follow-up. He had not consulted physicians again until the age of 30. Then he presented with severe thyroid eye disease, significant weight gain, hypothyroidism, and painful leg swelling. Levothyroxine was initiated, which stabilized his thyroid levels but had no effect on his exophthalmos and leg swelling. (*SKINmed*. 2024;22:215–216)

Physical examination revealed clubbing and swelling of the fingers and toes, with waxy indurated plaques on his legs. Treatment options were discussed with the patient; however, he opted not to be treated, because he only wanted medication to clear his lesions.

DISCUSSION

Thyroid dermopathy and acropachy are rare manifestations of Graves' disease, with incidences of 4% and 1%, respectively.[1] They occur almost exclusively in patients with ophthalmopathy (exophthalmos), and tend to appear in a chronologic order, first with ophthalmopathy, followed by dermopathy, and finally acropachy.[2] The triad of ophthalmopathy, dermopathy, and acropachy is rare and occurs in less than 1% of patients with hyperthyroidism.[3]

Although the exact etiology of extra thyroidal Graves' disease is unknown, the production of hyaluronic acid by fibroblasts is thought to occur via stimulation of thyrotropin receptors.[3] Additionally, tobacco use is a significant risk factor for developing exophthalmos and has been reported in many patients who develop dermopathy and acropachy.[2]

Acropachy is characterized by digital clubbing and swelling of soft tissue, with rare articular involvement of distal joints.[2] Thyroid dermopathy (pretibial myxedema) most commonly presents with nonpitting edema localized to the pretibial region, but it can also manifest as nodules, plaques, or elephantiasis-like edema.[3]

Dermopathy does not correlate with the severity of thyroid disease but could be an indicator of the severity of ophthalmopathy.[2,4] One report found that dermopathy occurred in 4% of patients with ophthalmopathy but was present in 13% of patients with ophthalmopathy requiring orbital decompression. Similarly, 53% of patients with acropachy required orbital decompression for their ophthalmopathy.[2]

Treatment of dermopathy involves topical steroids with occlusive dressings, compression bandages, intralesional steroids, and systemic corticosteroids. Case reports have also suggested pentoxifylline, gamma globulin, and rituximab with plasmapheresis as effective therapies.[3] Although no specific treatments exist for acropachy, local corticosteroids are used, and the immunosuppressive therapies directed toward dermopathy and ophthalmopathy have decreased acropachy as well.[2]

CONCLUSIONS

The triad of thyroid ophthalmopathy, dermopathy, and acropachy is rare and occurs in less than 1% of patients with Graves' disease. Tobacco use is a well-established risk factor for development of exophthalmos, which has been reported with high frequency in patients with dermopathy and acropachy. Encouraging cessation

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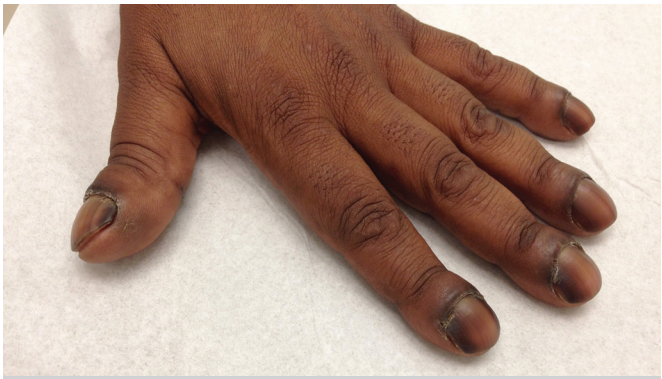

Figure 1. Clubbing and swelling of the fingers.

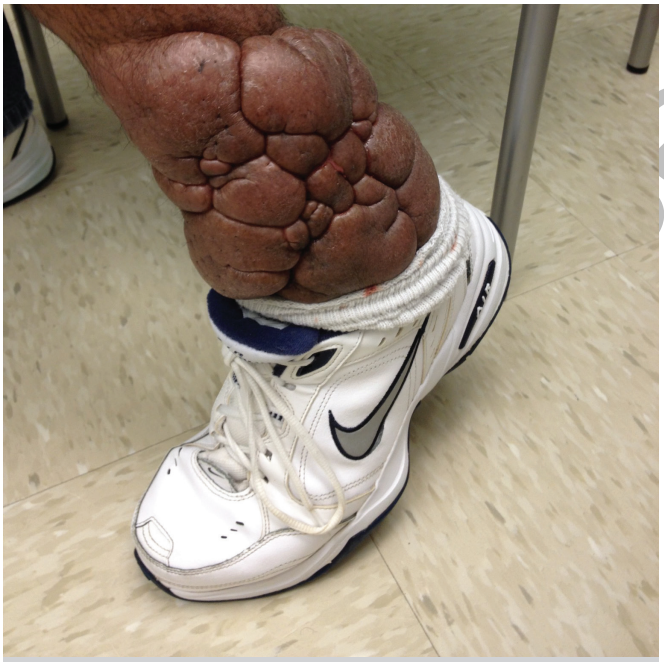

Figure 2. Waxy indurated plaques on the legs.

of tobacco use is crucial in addition to stabilizing thyroid levels in these patients. Dermopathy and acropachy also correlate with the severity of ophthalmopathy, and patients with these skin findings must be evaluated by an ophthalmologist, as they often require aggressive surgical intervention.

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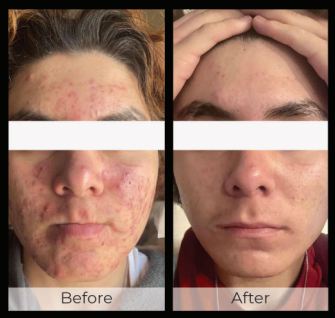

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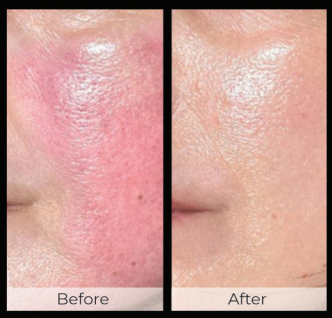

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William Abramovits, MD; Aditya K. Gupta, MD, PhD, FRCPC, Section Editors

Otezla™ (Apremilast 30-Mg Tablets)

William Abramovits, MD, FAAD;[1,2] Aditya K. Gupta, MD, PhD, FRCPC;[3,4] Kimberly Dawn Vincent, MD, FAAD[5]

ABSTRACT

Otezla™ was first approved on March 21, 2014 for the treatment of psoriatic arthritis, on September 23, 2014 for moderate to severe plaque psoriasis and on July 19, 2019 for the treatment of oral ulcers associated with Behcet's disease (BD). Apremilast is an inhibitor of phosphodiesterase-4, an enzyme involved in the pathogenesis of several dermatologic conditions. This review explores the potential utility of apremilast in the treatment of other unapproved dermatologic indications. (*SKINmed*. 2024;22:218–219)

DISCUSSION

Hidradenitis Suppurativa

Apremilast demonstrated a significantly superior clinical response versus placebo in a randomized controlled trial involving 20 patients with moderate HS. Fewer nodules and abscesses as well as a decrease in pain were reported, but there was no change in the Dermatology Life Quality Index (DLQI). Headaches and gastrointestinal adverse events (AE) did not result in dropouts.[4]

In a separate phase 2 open-label, prospective study that enrolled 20 patients with mild to moderate HS, apremilast proved to be safe and effective in the reduction of nodules and abscesses, pain, DLQI, HS clinical response (HiSCR30 and HiSCR50), and overall Sartorius score. AEs included diarrhea in 20%, nausea in 15%, and depression in 10% patients.[5]

A study comparing 15 HS patients treated with apremilast versus five HS patients on placebo, showed no statistically significant changes in inflammatory markers in HS lesions despite clinical improvement in those treated with apremilast.[6]

Occasional case reports about the use of apremilast for HS in real life add to the value of properly conducted trials.[7]

Atopic Dermatitis

No appreciable benefit in Eczema Area and Severity Index (EASI) was observed in a phase 2 randomized, double-blind, placebo-controlled trial of moderate to severe AD patients.[8] Expert opinions point out negative results for apremilast in AD.[9]

Vitiligo

Apremilast did not bring additional statistically significant benefit to narrow band ultraviolet B (NB-UVB) in treating vitiligo. In a single-center, randomized, placebo-controlled study that included 80 patients (40 in each group), both groups saw the Vitiligo area scoring index (VASI) decrease similarly at 24 weeks and 1 year.[10]

In a report including 13 patients with adult-onset vitiligo who had not responded to other systemic treatments, "some evidence of repigmentation" was noticed in 8 (61.5%) patients.[11]

Alopecia Areata

A report of four patients with extensive AA suggested a potential for success with aprimelast.[12] However, in a separate 6-month

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study using monthly Severity of Alopecia Tool (SALT) scoring, no sustained AA improvement was shown in four out of five patients.[13]

Palmoplantar Pustulosis

A multiple month case series involving eight patients with palmoplantar pustulosis evaluated via Investigator's Global Assessment (IGA) score suggested benefits.[14] One case report of refractory palmoplantar pustulosis treated successfully with apremilast was described.[15]

Pemphigus Vulgaris

A 62-year-old patient with recalcitrant chronic pemphigus vulgaris received apremilast for 32 weeks. Blistering ceased, lesions healed, and the effect was reported to be "long-lasting."[16]

Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) Syndrome

Apremilast "stabilized skin and joint symptoms" in a 24-year-old woman who presented with palmoplantar pustulosis and sternoclavicular joint involvement, prior treatments included with methotrexate, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), etanercept, adalimumab, ustekinumab, and secukinumab.[17,18]

Lichen Planus

Out of three patients WITH recalcitrant oral lichen planus, one patient reported 'effective' treatment with apremilast.[19]

CONCLUSIONS

Apremilast has the potential to affect positively a variety of inflammatory skin diseases. The analysis of recent literature emphasizing unapproved indications suggests a value for HS, palmoplantar pustulosis, pemphigus vulgaris, SAPHO syndrome, and oral lichen planus. No probable value was discovered for AD, vitiligo, and AA. Its cost, adverse events, and lack of properly conducted studies should discourage the random trial of apremilast, particularly where disease pathogenesis cannot be supported by the MoA of apremilast.

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CASE STUDY

Vesna Petronic-Rosic, MD, MSc, MBA, Section Editor

A Case Report of Red Lunulae after Liver Transplantation

Gaurav Agnihotri, MD; Amy Z. Xu, MD, MA

A 50-year-old man with a history of alcoholic cirrhosis status post liver transplant about 3 months prior to consultation presented with abnormal appearing fingernails for the past month. He had noted discoloration of his fingernails, which was initially dark pink and asymptomatic. He denied trauma or any new contactants to the nails. (*SKINmed*. 2024;22:221–222)

On examination, all the right fingernails and the third to fifth left fingernails showed true red lunulae (Figure 1). A red vascular crescent appeared over the proximal lunulae and was visible through the cuticle (Figure 2). There were also horizontal ridges at the distal edges of the red lunulae.

We diagnosed red lunulae secondarily attributed to the recent liver transplant. We advised that the changes to the nails would likely grow out with time and suggested that he avoid trauma or manipulation of the nails. At the 4-month follow up, the discoloration had resolved with distal nail dystrophy (Figures 3 and 4). The proximal nail fold appeared normal with mild opaqueness to the nail plate.

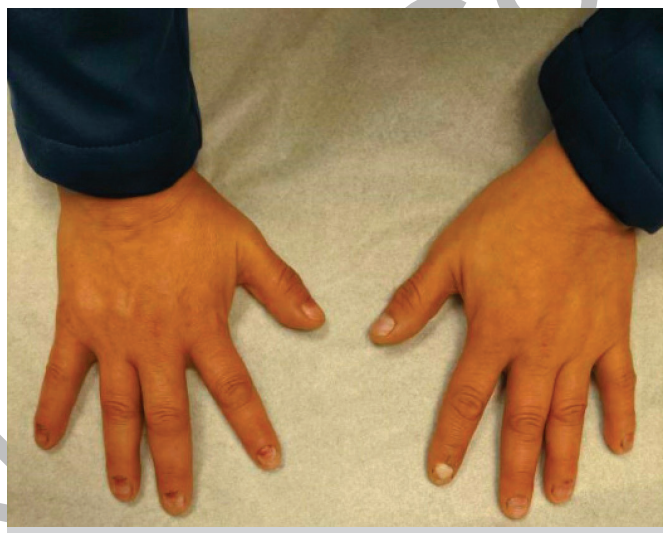

Figure 1. Fingernails with red lunulae on initial presentation.

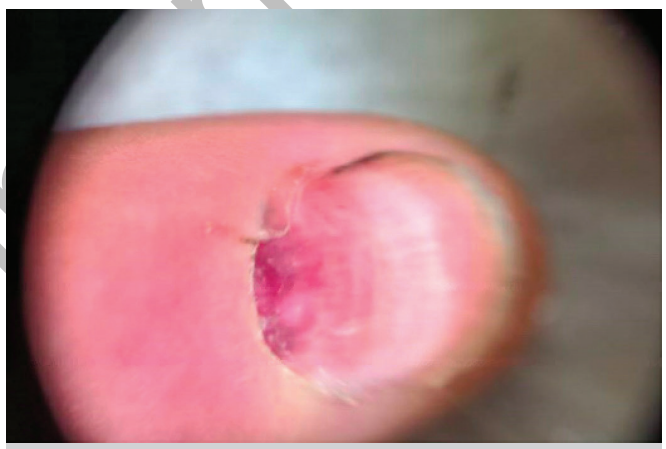

Figure 2. Onychoscopy of red lunulae on the right thumbnail.

DISCUSSION

The red lunula was initially described in the 1950s in patients with cardiovascular disease and alopecia areata.[1,2] As the name describes, "red lunula" is an erythema that substitutes the usual white lunula; occasionally, there could be a peripheral white band distal to the red lunula. It usually affects the thumbs, where the lunulae are most commonly visible but has been reported to affect all fingernails and toenails.[3] The erythema blanches if the nail plate is pressed.

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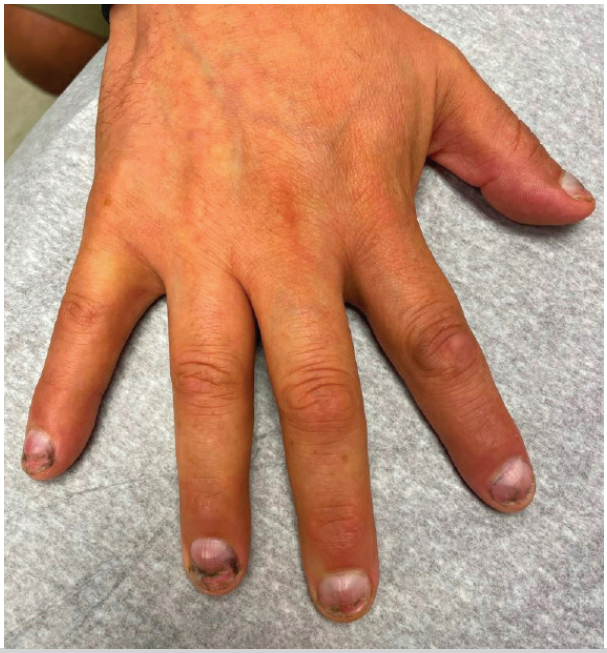

Figure 3. Resolved red lunulae with distal nail dystrophy on the right hand at 4-month follow-up.

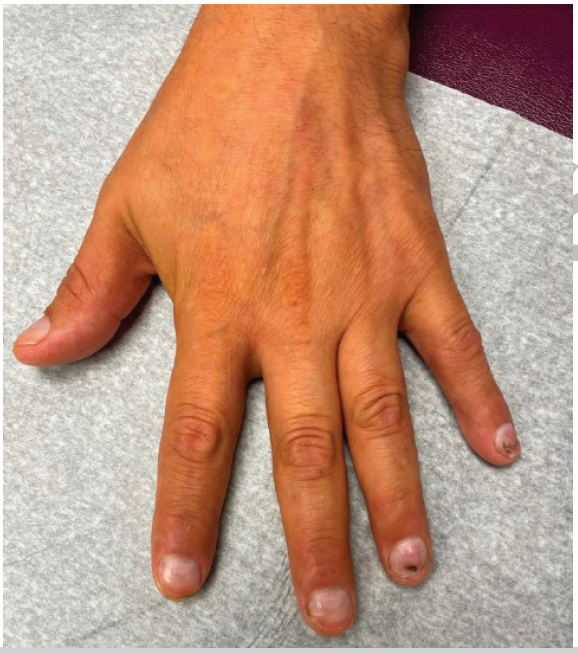

Figure 4. Resolved red lunulae with distal nail dystrophy on the left hand at 4-month follow-up.

Red lunulae have been described in various dermatologic entities, such as alopecia areata, vitiligo, lichen sclerosus et atrophicus, psoriasis, and twenty-nail dystrophy or trachyonychia.[3] It could also occur in diseases of the connective tissues, such as rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, and Sjogren's syndrome.[3] To our knowledge, this patient is the first instance of red lunulae associated with liver transplantation. The only other reported red lunulae associated with solid organ transplantation appeared in a heart transplant patient.[4] Hematopoietic stem cell transplant also has been associated with red lunulae.[5] Various other endocrine, gastrointestinal, infectious, hematologic, neoplastic, and pulmonary diseases have been associated with red lunulae, although the significance of the associations is yet to be determined.

The first histopathologic examination of red lunulae in a patient with chronic obstructive pulmonary disease, diabetes, and cirrhosis was reported in 1989; however, the biopsy did not reveal any abnormalities.[6] In 2013, another biopsy of a red lunula in a patient with erythrocytosis demonstrated increased vascularity in the papillary dermis of the distal nail matrix.[7]

The etiology of red lunulae remains unknown. Several theories include increased arterial blood flow, capillary proliferation, or vasodilation.[1,7] The duration of red lunulae is variable, as there have been reports of red lunulae persisting for years, while some faded over weeks.[8,9]

CONCLUSIONS

The present case report highlights a novel systemic association for an uncommon yet distinctive nail condition.

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CASE STUDY

Chronic Blepharitis: Consider Tinea Blepharo-Ciliaris

Meriem Ouederni, MD;[1] Anissa Zaouak, MD;[2] Fehmy Nefaa, MD;[1] Sonia Anane, MD;[3] Monia Cheour, MD[1]

A 7-year-old girl with a history of being in contact with a cat was referred to our department due to her 1-month unilateral blepharitis that was initially treated as a herpetic infection without amelioration. She experienced itching and loss of her right eyelashes (Figure 1). Her visual acuity was 20/20. The slit lamp examination revealed anterior blepharitis with madarosis, broken eyelashes, and lesions in right lower eyelid, while the left eyelids were normal. (*SKINmed*. 2024;22:223–224)

CASE 1

We suspected fungal infection. Dermatoscopic examination revealed scales, bent and broken hair, and Morse-code hair (interrupted hair) in both eyes, with the near absence of her right eyelashes (Figure 2). Mycologic examination confirmed a pathogenic fungus *Microsporum canis* infection, ensuing tinea blepharo-ciliaris in both eyes (Figures 3A and 3B). Treatment with griseofulvin 500 mg once a day and topical econazole for 6 weeks led to lessening eliminate of the infection.

CASE 2

A 23-year-old woman with a history of being in contact with a cat was referred to our department for bilateral chronic blepharitis

Figure 1. Blepharitis with loss of right eyelashes and broken hair.

Figure 2. In the first patient, trichoscopy of left eyelashes reveals scales with bent hair and Morse code-like hair (Dermlite DL4, magnification ×10).

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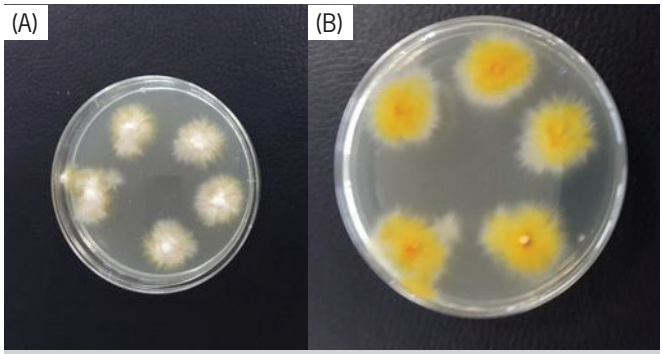

Figure 3. (A) Fungal culture reveals white fluffy colonies with radial gooves. (B) The reverse color is a bright golden yellow.

persisting for 3 months and resistant to topical steroids. She had itching, with the presence of scales on her eyelashes. Her visual acuity was 20/20, but the slit lamp examination revealed anterior blepharitis. Dermatoscopic examinatiosn revealed bilateral scales, bent hair, and Morse code-like hair (interrupted hair). Mycologic examination confirmed a *Microsporum canis* infection. The fungal infection cleared with oral administration of griseofulvin, 1,000 mg, once a day and topical econazole administered for 6 weeks.

DISCUSSION

Blepharitis may be associated with systemic diseases or caused by microbial infections. Characteristic findings include red eyes, blurred vision, itching, tearing, irritation, and photophobia.[1] *Microsporum canis*, a zoophilic dermatophyte, rarely induces blepharitis and tinea blepharo-ciliaris in humans.[2]

The first patient exhibited chronic blepharitis with loss of her eyelashes, while the second had chronic blepharitis with scales. *Microsporum canis* commonly causes tinea capitis, with rare involvement of the palpebral area.[2–5] The differential diagnosis probably includes atopic or seborrheic dermatitis, especially without involvement of other anatomic regions, particularly the scalp.[6]

Dermatophytosis should be considered if scaly skin lesions with inflammatory signs and an active spreading border affect the eyelid margins, causing blepharitis and dysfunction of the Zeiss, Moll, and Meibomian glands.[5,6] In the first patient, lesions and anterior blepharitis without involvement of other body areas were observed, leading to a misdiagnosis of a herpetic infection. For the second patient, chronic blepharitis was misdiagnosed as dermatitis, and the patient was treated with topical steroids.

Trichoscopy is a valuable noninvasive tool for the rapid diagnosis of tinea blepharo-ciliaris, although it does not identify the responsible agent.[7] The definitive diagnosis relies primarily on a fungal culture. In the first patient, dermatoscopy allowed the diagnosis of tinea blepharo-ciliaris prior to the loss of her eyelashes, while in the second patient, tinea blepharo-ciliaris was suspected based on the presence of perifollicular scales and bent hair. Trichoscopic features include bent and broken hair, Morse code-like hair, and scales. Therapeutic success is judged with the disappearance of dystrophic hair and lessened scaling.[8]

CONCLUSIONS

Both griseofulvin and terbinafine are effective therapies for tinea blepharo-capitis caused by *Microsporum canis*.[9] The animal must also be treated by a veterinarian. Finally, if chronic blepharitis persists, consider dermatophyte infection.

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CASE STUDY

H Syndrome: Three New Cases from Morocco

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A 19-year-old girl presented with symmetric and bilateral hyperpigmentation, an indurated lesion that initially appeared on the axillary fold at the age of 14, which then extended to the lower back, anterior aspect of both thighs, and popliteal fold. No hypertrichosis was observed (Figure 1).The patient was the youngest of the four children, born from the first-degree consanguineous marriage. She was born at full term and weighed 2,420 g at birth. No similar patient was present in the family. The patient experienced delayed motor acquisition and stature growth (3rd percentile) until the age of 4. Right hypoacusis was diagnosed at the age of 6. She developed hallux valgus, flexion contracture of the fingers and toes, barrel deformity of the anterior thorax, and recurrent fever. The laboratory tests, including fasting blood glucose, triglycerides, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were normal. Her abdominal, pelvic, and transthoracic ultrasound scans were normal, with no hepatosplenomegaly, lymphadenopathy, or cardiac abnormalities. Histologic analysis demonstrated patchy acanthosis of the epidermis, with orthokeratotic hyperkeratosis. Keratinocyte hyperpigmentation and spongiosis at certain areas were observed with moderate inflammation because of the infiltration of lymphocytes, histiocytes, and plasma cells. Immunohistochemical analysis showed macrosialin (CD68+) and common gamma chain (γ_c) CD132. Germline *mutations in* the *SLC29A3* gene were not analyzed. The patient was prescribed dermocorticoids with depigmentation therapy, which demonstrated moderate clinical evolution. (*SKINmed*. 2024;22:225–227)

PATIENT 1

A 6-year-old boy presented with hyperpigmented, indurated, and symmetric patches on anterior aspect of the thighs and pelvic and lumbar regions, without hypertrichosis, which appeared at the age of 3. These manifestations were associated with delayed growth (-2nd percentile), abdominal distension, lymphadenopathy, and recurrent fever (Figure 2).

The patient was born at full term without incident from the first-degree consanguineous marriage. No similar patient existed in the family. His psychomotor development was normal.

Patient's laboratory investigations demonstrated a significant inflammatory syndrome. His CRP level was 56 mg/L and ESR was 112 mm/h; however fasting blood glucose and triglycerides were normal.

The abdominal ultrasound revealed splenomegaly without hepatomegaly or lymphadenopathy; no cardiac anomalies were observed in the transthoracic ultrasound scans. Histologically, the epidermis indicated acanthosis with basal hyperpigmentation, and the dermis was fibrous with infiltrate comprising mononuclear cells, lymphocytes, histiocytes, and some plasma cells. The *SLC29A3* gene mutations were not analyzed.

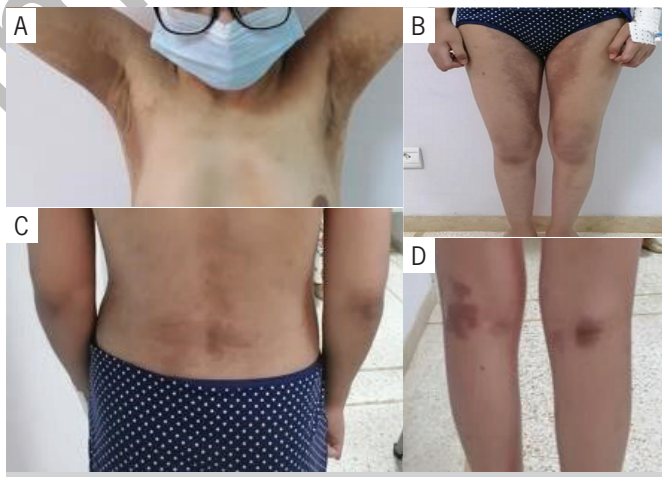

Figure 1. Hyperpigmented and indurated lesions of (A) axillary fold, (B) thight, (C) lower back, (D) popliteal fold

PATIENT 2

An 11-year-old boy, born from first degree consanguinity, presented with confluent, nonpruritic, and infiltrated hyperpigmented macules. The macules appeared at 3 years of age, and were present bilaterally and symmetrically on the legs, trunk, and

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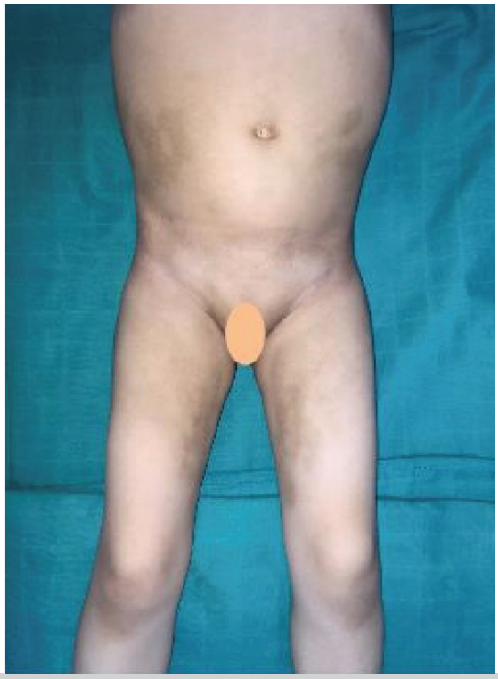

Figure 2. Hyperpigmented, indurated and symetrical lesions

face (Figure 3). The clinical manifestations were associated with hypertrichosis, delayed stature, and right hypoacusis. The patient was initially diagnosed as having mastocytosis.

The laboratory results established an inflammatory syndrome with a CRP level of 42.3 mg/L and an ESR of 94 mm/h, without hyperglycemia.

The abdominal ultrasound demonstrated homogeneous hepatomegaly and multiple bilateral inguinal adenopathies. The scrotal ultrasound was normal.

The histologic analysis indicated acanthosis and orthokeratotic epidermis without dysplasia. The papillary dermis was edematous, and the reticular dermis showed dense perivascular inflammatory infiltrate rich in lymphocytes, probabilistic neural network (PNN), and mast cells.

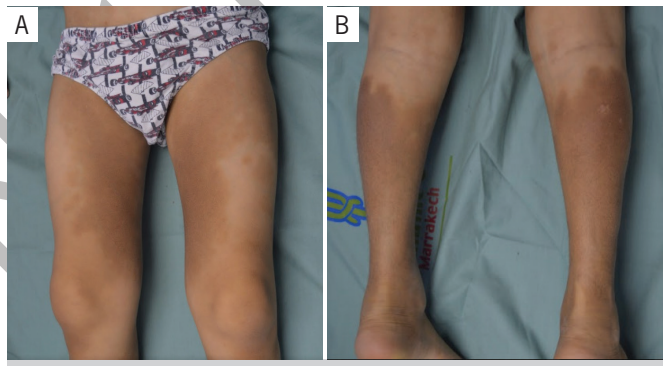

Figure 3. Hyperpigmented and symetrical lesions

Considering the clinical and paraclinical profile, the diagnosis of H syndrome was confirmed in all the patients. All were prescribed local dermocorticoids, resulting in good clinical evolution.

DISCUSSION

H syndrome is an autosomal recessive disorder with systemic manifestations.[1] First described in 2008, the term "H syndrome" was created verbally from the alliteration of its most common clinical features: hyperpigmentation, hypertrichosis, hepatosplenomegaly, hypoacusis, heart anomalies, hypogonadism, low height, hyperglycemia/diabetes mellitus, and hallux valgus/flexion contractures.

Recent studies have suggested that H syndrome must be considered as a new inherited form of histiocytosis.[2]

H syndrome, which appears to be more common in patients of Arabic origin,[1] is described to have global presence and must be included in the differential diagnosis of patients with small stature and systemic inflammation, especially if accompanied by characteristic skin manifestations.[3]

The slow and progressive evolution of H syndrome could lead to misdiagnosis or delayed diagnosis. Certain features of H syndrome overlap with morphea, plasma cell panniculitis, Muckle–Wells syndrome (MWS), and polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome in childhood.[4]

The discussed three patients had hyperpigmented and indurated bilateral and symmetric lesions, although two of these had no hypertrichosis. All the patients had low stature, hallux valgus, hearing loss, and recurrent fever.

In the literature, in a series of 14 patients collected from studies between 2015-and 2021 (table 1), 57.14% were men, the average age at occurrence of initial manifestations was 6 years, and the average age at diagnosis was 16.25 years, with an average delay of 10.25 years. In addition, 85.7% of patients had bilateral and symmetric hyperpigmentation, 64.28% had hypoacusis, 57.14% had delayed stature, 85.71% had flexion contracture of the fingers or toes, and 42.85% had gynecomastia and a scrotal mass.

Considering laboratory investigations, 71.42% of patients had microcytic anemia, 100% had high CRP levels and an elevated ESR, 28.57% had thrombocytosis, 21.42% had elevated follicle-stimulating hormone (FSH)/luteinizing hormone (LH) levels, 21.42% had elevated testosterone, and 7.14% had elevated fasting

plasma glucose levels. All patients had the *SLC29A3* mutation. Hematologic anomalies were observed in two patients (Table 2).

Radiologic examinations established that 50% of patients had hepatomegaly, 42.85% had splenomegaly, 14.28% had lymphadenopathy, 7.14% had cardiac abnormalities, and 21.42% had nephropathy (Table 2).

In addition to the above-mentioned results, considerable interfamilial and intrafamilial clinical variability was determined, with no clear correlation between phenotype and genotype. In a recently conducted series of studies, two identical twins presented with H syndrome at opposite ends of the phenotypic spectrum.[5] One of the twins developed a severe phenotypic profile with large skin patches, skeletal and systemic involvement, hypogonadism, and marked gynecomastia; however, the other sibling showed a considerably milder profile, with no systemic involvement, except for arthritis and mild gynecomastia but had phenotypic diversity. In the present study as well, patient 3 had an extreme phenotypic profile, with infertility because of azoospermia, whereas his brother had only mild foot deformities.[5]

Histologically, skin lesions in our patients evidenced deep dermal inflammation, with the above-described acanthosis and orthokeratotic epidermis.

The key to diagnosis, in addition to laboratory, histologic, and radiologic investigations, is a molecular genetic analysis that identifies germline *mutations in* the *SLC29A3* gene.[3] Unfortunately, this analysis was not performed in our patients because of lack of resources.

Different studies have tried various treatment modalities for H syndrome, generating varying responses. Corticosteroids are prescribed most frequently as a monotherapy or a combination therapy with methotrexate, cyclosporine, and colchicines, demonstrating partial or temporary lessening of manifestations. Besides, the interleukin 6 (IL-6) receptor antagonist to cilizumab, as a monotherapy or a combination therapy, has shown promising results,[6–8] reducing systemic inflammation; however, it could not control all clinical manifestations. Additional treatment modalities to consider are combination therapy with biologicals and other immune suppressants. Improved identification and understanding of pathophysiology could help reach timely diagnosis and determine better treatment strategies.[3]

CONCLUSIONS

H syndrome is suspected in patients with typical skin manifestations, systemic abnormalities, and endocrine pathology. The most intriguing feature of this syndrome is the range of manifestations, varying from mild to very severe indications. Molecular genetic analysis is the key to its diagnosis. In the reported three patients, dominant skin involvement made the diagnosis possible.

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CASE STUDY

Giant Cerebriform Nevus Lipomatosus Cutaneous Superficialis with Diffuse Lipomatosis: An Unusual Presentation on the Neck

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A 25-year-old man presented with gradually increasing swelling of 15 years' duration on the left side of his neck. There had been occasional foul-smelling discharge from the swelling. Local examination revealed an 8 cm × 5 cm oblong-shaped, yellowish to skin-colored, soft, cerebriform swelling. There were multiple open comedones (Figure 1a). The surrounding skin had small and soft skin-colored papules. On palpation, there was no ulceration, tenderness, induration, or bag of worms. A scar from the past surgery was visible. Systemic examination was unremarkable. The differential diagnosis demonstrated plexiform neurofibroma and nevus lipomatosus cutaneous superficialis (NLCS; Figure 2). (*SKINmed*. 2024;22:228–229)

Histopathologic examination revealed papillomatosis, irregular acanthosis, and follicular plugging of the epidermis. Aggregates of mature adipocytes were discovered around the dermal blood vessels and eccrine glands, and between the collagen bundles, which confirmed the diagnosis of nevus lipomatosus superficialis.

Magnetic resonance imaging (MRI) confirmed the findings of a large fat attenuation lesion in the subcutaneous tissue on the anterior left triangle of the neck, surrounding the parotid gland and extending into the sublingual and parapharyngeal regions. This findings suggested diffuse lipomatosis with NLCS (Figure 3).

The patient underwent surgical excision of the mass, which abutted the facial nerve and pre-styloid parapharyngeal space, medially up to the strap muscles. Adhesions and the fibrous tissue were present because of the past surgical procedure. The involved skin was also excised, and primary closure was carried out. A significant reduction in the size of the swelling was observed (Figure 1b). The histopathologic study indicated the lobules of mature adipose tissue, suggesting the diffuse lipomatosis surrounding the salivary glands.

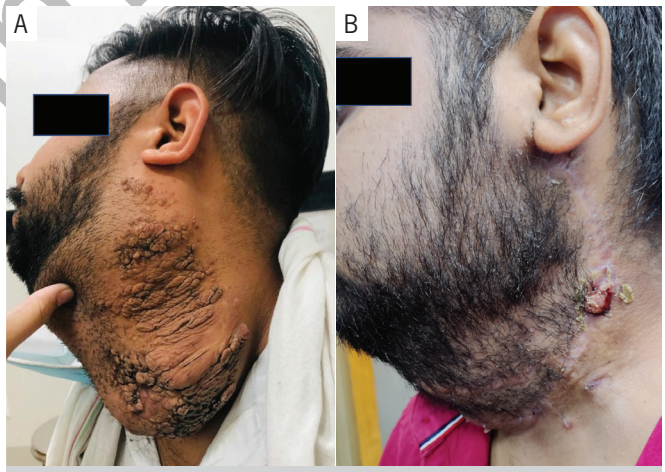

Figure 1. (A) The patient with an 8 cm × 5 cm oblong-shaped, yellowish to skin-colored, soft, cerebriform swelling on the left side of his neck, with comedones on the surface. (B) Post-surgical excision.

DISCUSSION

NLCS is a rare hamartomatous entity with unknown pathogenesis. It could represent a reactionary process to the degeneration

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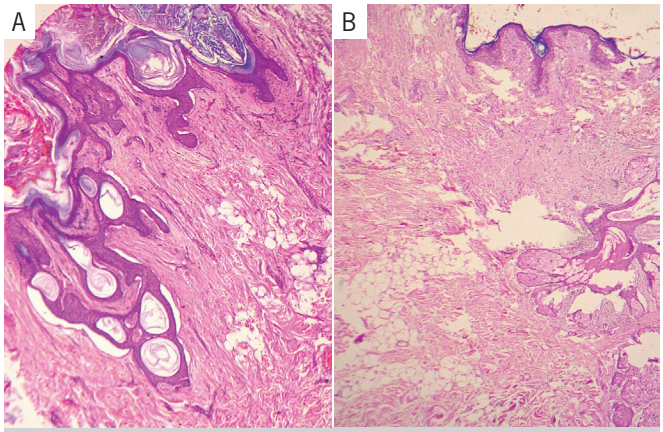

Figure 2. (A and B) Hematoxylin and eosin-stained sections indicating hyperkeratosis, focal papillomatosis, and irregular acanthosis of the epidermis accompanying horn cysts. The dermis contains mature adipose tissue infiltrating the dermal collagen.

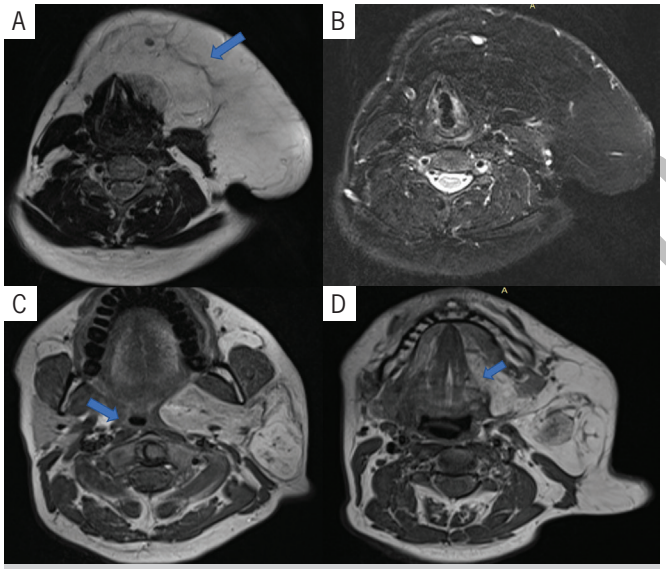

Figure 3. MRI findings. (A) Axial T2-weighted image (T2W1) revealing a large fat attenuation lesion involving the subcutaneous tissue in the anterior and left triangle of the neck, causing its thickening. (B) Uniform suppression on fat-suppressed images. (C) Enlarged superficial and deep lobes of the left parotid gland involving the lesion and indenting the left parapharyngeal wall. (D) The lesion extends into the left sublingual space.

of the elastin. Recent electron microscopic studies have confirmed the presence of matured adipocytes around the dermal vessels and the subsequent differentiation into mature fat.[1,2]

The classic-type NLCS, as in our patient, has a predilection for the pelvic girdle and gluteal, sacral, or lumbar regions; however, our patient had a giant clinical presentation on the neck. Although giant NLCS has been reported in the pelvic girdle area, only one patient has been presented with a giant lesion on the neck.[3]

More often, NLCS is asymptomatic, although with a foul-smelling discharge. Ulceration of lesions following external trauma or ischemia and compression neuropathies has been reported. Case reports have revealed the association of NLCS with diffuse lipomatosis and lipoma.[1] Some lesions may have unusual morphology, such as comedo-like plugs, also observed in our patient, hyperpigmentation, or overlying hypertrichosis.[4]

Treatment is for cosmetic reasons or associated findings. Excision is generally curative. Other treatment options include cryosurgery and ablative laser surgery with CO_2 or diode.[5]

CONCLUSIONS

Our patient highlights rare features of a classic NLCS, including a giant presentation at an unusual site, presence of foul-smelling discharge, and association with diffuse lipomatosis and comedo-like plugs on the surface. An early diagnosis could endure a more conservative resection of the tumor.

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CASE STUDY

Facial Dermatitis Herpetiformis

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A 34-year-old African-American woman with a past medical history of human immunodeficiency virus (HIV) and hypertension presented to the clinic with a blister that was appearing about once a month on her nose or cheeks over the past 8 months. The blister was occasionally pruritic and would resolve spontaneously. At the time of presentation, the patient had only post-inflammatory hyperpigmentation on her nasal dorsum. The patient had photos of the blister on her phone to show what it originally looked like (Figure 1). (*SKINmed*. 2024;22:230–231)

Based on the morphology and distribution of the lesion, a dermatitis herpetiformis (DH) panel was ordered. The patient's laboratory investigations established that immunoglobulin A (IgA) antibodies against tissue transglutaminase (TG2) were less than 2 U/mL and her IgA level was 211 mg/dL—both findings were within normal limits; however, she had an elevated level of IgA against deamidated gliadin at 23 units (normal range: 0–19 units). Further serologic findings indicated an elevated level of antibodies against epidermal transglutaminase (TG3) at 26.1 AU/mL (normal value: <16 AU/mL). A diagnosis of DH was made based on the patient's serologic findings. The patient was advised to adhere to a strict gluten-free diet, and was referred to a gastroenterologist. The patient reported 8 month later that no new blisters had developed after she started a gluten-free diet.

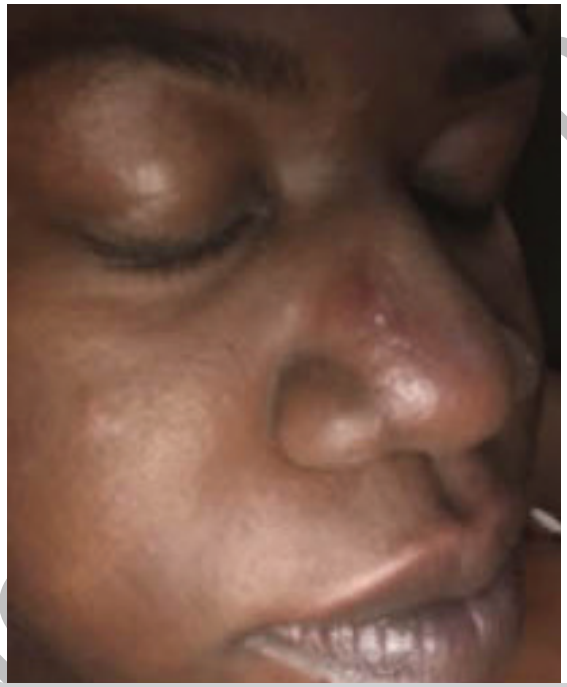

Figure 1. Dermatitis herpetiformis—an isolated vesicle on the nasal sidewall (image taken from patient's phone).

DISCUSSION

There have been five other documented case reports of DH isolated to the face. These patients were diagnosed by direct immunofluorescence (DIF) instead of serologic testing (Table 1). While these patients presented with active lesions for biopsy, patients may also present without any clinically evident lesions.

The current standard criterion for the diagnosis of DH is DIF of perilesional skin, showing granular deposition of IgA within the dermal papillae.[5] If a patient presents without lesions, the clinician must be cognizant of the distribution pattern of DH to know when to prescribe serologic testing. Antibodies against TG2 are important in the pathogenesis of celiac disease (CD), and thus DH; however, such antibodies can be negative and a diagnosis of DH can still be made if there is evidence of antibodies against TG3.

TG2 plays a critical role in the pathogenesis of CD.[7] TG2 deamidates gliadin, a digestive product found in gluten; this product creates antigen and forms antibodies against TG2, and deamidated gliadin. These antibodies contribute to crypt hyperplasia and villous atrophy in the gut. Antibodies against TG3 occur

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Table 1. Incidents of Facial Dermatitis Herpetiformis Diagnosed through Direct Immunofluorescence or through Serologic Evidence of Antibodies to Gliadin or Tissue Transglutaminase[1]

Study	Location of Lesions on the Face	Diagnostic Procedure
Komura and Imamura (1977)[2]	Mouth and eyelids	DIF, histology
Helander and Jansen (1987)[3]	Eyelids and cheeks	DIF, antibodies to gliadin
Kaplan et al. (2004)[4]	Forehead, nose, cheeks, and chin	DIF
Kawakami et al. (2008)[5]	Perioral and right ear	DIF, histology
Taglia and Hossler, (2014)[6]	Forehead	DIF, antibodies to TG2

through spreading of epitope and are pathogenic in the cutaneous lesions of DH.[8] Antibodies against TG2 have been demonstrated to be the most sensitive marker in the diagnosis of CD and DH with sensitivities of 98.2% and 89.1%, respectively.[7,9] While screening for TG2 antibodies on serology remains the most common course for clinicians to diagnose DH, TG3 antibodies can be used as well in patients where TG2 antibodies are absent, but clinical suspicion is high. In a study comprising 54 pediatric and 173 adult patients with CD, it was demonstrated that 20% of patients with DH were negative for antibodies against TG2 but positive for antibodies against TG3.[10] The prevalence of antibodies against TG3 was only 50% in adult patients and 11.1% in pediatric patients, which is why, probably, this marker alone is not used in routine diagnosing of CD, and thus DH.[4] If present, antibodies against TG3 have a sensitivity of 50%–100% and a specificity of 93%–100% for DH.[11] Our patient represented a unique instance in which titers were negative against TG2 but positive against TG3, demonstrating why a high degree of clinical suspicion, based on recognizing the facial distribution of DH, is necessary for appropriate diagnostic work-up.

Dapsone prescribed for three days could be sufficient to stop itching and significantly reduce skin lesions in DH.[1] Although dapsone is effective for clearing cutaneous lesions, it has no effect on the gastrointestinal pathology of the disease. Importantly, there is a clear relation between CD and enteropathy-associated T-cell lymphoma. Ultimately, the only course to prevent the intestinal pathology of CD and the cutaneous manifestation of DH is by adhering to a strict gluten-free diet.[6]

CONCLUSIONS

Dermatitis herpetiformis, the cutaneous manifestation of CD, results in the formation of pruritic vesiculobullous (VB) lesions on extensor surfaces, such as the elbows and knees as well as on the scalp, back, and buttocks. Isolated facial involvement is a rare presentation of DH and can lead to misdiagnosis, such as herpes simplex infection.[1] The standard criterion for diagnosing DH requires a biopsy of uninvolved skin adjacent to an active lesion showing granular IgA deposition within the dermal papillae on DIF.[5] As DH is a waxing and waning dermatosis that can result in patients presenting when lesions are absent, clinicians must have a high index of suspicion to recommend a necessary work-up. The classic finding of IgA against TG2 is not always present, and clinicians must be aware that antibodies against TG3 may be the only available information to diagnose DH.[10]

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CORRESPONDENCE

Snejina Vassileva, MD, PhD, Section Editor

Skin Cryobranding—A Worrisome Trend among Bulgarian Children

Kristina Milkova, MD;[1] Jana Kazandjieva, MD, PhD;[2] Razvigor Darlenski, MD, PhD[3,4]

Skin branding, the process of creating a permanent scar by burning or freezing the skin of a living human or animal with a very hot or freezing iron, dates back to the Roman Empire. It has been used for marking complete slaves, for punishment, religious initiation, as a treatment procedure, and, most recently, for aesthetic purposes.[1–3]

A 13-year-old Caucasian girl presented with a painful bullous eruption on the volar forearm (Figure 1A). A day prior to the occurrence of eruption, she had applied a diffuser ring deodorant spray (Figure 1B) for 5 seconds to the skin surface, which resulted in immediate skin blanching and pain. The patient had no relevant present or past medical history, except her consenting that this was a common practice among her peers to create a "rosette tattoo" for aesthetic purposes.

Clinical examination revealed sharply demarcated erythematous annular plaque with lesions and bullae. Treatment with topical hydrocortisone butyrate 0.1% cream twice daily for 10 days, following the initial blister evacuation and concomitant emollient and sun protection, resulted in significant diminishing of lesions, leaving erythematous rosette-like hyperpigmentation (Figure 1C). After 1 month, only slight erythema was visible (Figure 1D).

Seven weeks later, patch testing was performed with Finn Chambers®, a patch test device, according to the International Contact Dermatitis Research Group (ICDRG) criteria, with the European baseline and fragrance series (Chemotechnique, Vellinge, Sweden), with no positive reactions on interpretations on days 2, 3, and 7.

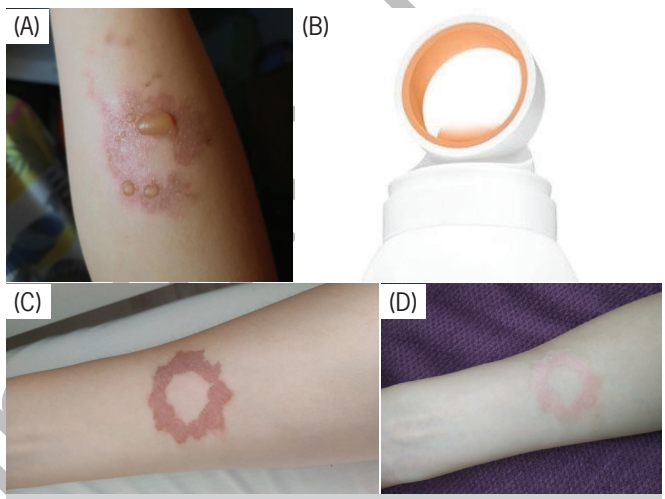

Figure 1. (A) Development of acute erythema, edema, lesions, and blisters on the skin of the volar forearm. (B) Diffuser ring deodorant spray used for freeze branding. (C) Erythema and hyperpigmentation at the freeze site, on day 10 of the initiation of treatment. (D) Slight residual erythema visible on day 30.

DISCUSSION

Skin cryobranding (freeze branding), first introduced in the 1960s for marking living stock as an alternative to hot-iron branding, has acquired popularity as a body art in Western societies.[1] Substance abuse, promiscuity, and even homicide/suicide behavior have been discovered in subjects undertaking body branding.[4] The intentional self-injury in the present patient is not associated with behavioral disturbance, rather revealing a trendy ritual among Bulgarian teenagers as a symbol of personal identity.

Practices used for body branding include mechanical trauma, hyperthermal and hypothermal stimulus (cryobranding), chemical agents, electrocautery, lasers, and solar energy (focusing lens and a light source).[5] The unique source of hypothermal damage in our patient was a diffuser ring deodorant spray, which has not been reported in the past.

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CONCLUSIONS

Complications of body branding include secondary skin and systemic infection, keloid and contracture formation, and neoplastic transformation.[3,5,6] Despite being uncomplicated, the present patient is important because it reveals a novel worrisome practice among Bulgarian teenagers.

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Comment on "Case Presentation: Monkeypox"

Rujittika Mungmunpuntipantip, MD;[1] Viroj Wiwanitkit, MD[2]

To the Editor:

We share our ideas on the paper, "Case Presentation: Monkeypox."[1] According to the authors, monkeypox is a rare viral disease that initially surfaced in West and Central Africa, and is largely spread to humans from animals. The disease spread from the African continent and made its way to the United States in 2003.[1] An important factor is the clinical presentation of monkeypox. Its diagnosis might occasionally be difficult because of asymptomatic or slightly symptomatic manifestations without fever and hidden skin lesions;[2] however, the mainstay of monkeypox diagnosis is laboratory examination.

GOLD STANDARD

In general, the gold standard for the diagnosis of monkeypox is molecular diagnostic testing. Clinical samples are typically collected from vesicular lesions, and a specific real-time reverse transcription polymerase chain reaction (RT-PCR) assay is recommended among several techniques. The specific RT-PCR assay is demonstrated to be superior to a nonspecific orthopoxvirus assay;[3,4] however, laboratory quality control is still an issue.[5] According to the past reports, many laboratories have difficulty in diagnosing monkeypox using PCR and false positive results are possible. In order to improve the diagnostic testing, the laboratory must adhere to the basic laboratory quality management guidelines, beginning with the pre-analytic phase (specimen collection).

CONCLUSIONS

It is necessary to use the standard diagnostic test kit. External quality assurance and international standardization are also vital prerequisites. In addition, due to the likelihood of inaccurate laboratory results, it is crucial to repeat the test to confirm the high probability that the patient has monkeypox.

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Dermatology in Correctional Health: A Pilot Survey Study

Aneesh Agarwal, MBA;[1] Samir Kamat, BA;[1] William Gansa, BA;[1] Saahil Patel, BS;[2] Jun Lu, MD;[3] Jackleen S. Marji, MD, PhD;[4] Jacob Appel, MD, JD, MPH[1]

To the Editor:

Dermatologic care of incarcerated patients can be logistically complex, with potentially disparate patient outcomes.[1,2] Greater understanding of the associated facilitators and barriers may lead to increased care quality and provider awareness among this often underserved patient population. We distributed a survey among dermatologists involved in the care of justice-involved patients. The survey had queries about the setup of correctional dermatology clinics, clinicians' demographics, commonly treated dermatologic conditions, the scope of services, and general facilitators and barriers to care.

RESONSES

Respondents included 10 dermatologists, each having experience of more than 6 years in correctional dermatology (Table 1). For care delivery models, half reported in-person and the rest reported a hybrid of telehealth and in-person care. Of the included dermatologists, 80% reported being attending physicians or residents supervising or providing correctional care, with none reporting the involvement of advanced practice providers (physician assistants or nurse practitioners). Monthly operating time ranged from 2 to 144 (median 14) hours. Total patients examined every month varied, with 11–20 and >30 patients being the most selected response. Dermatologic conditions spanned multiple therapeutic domains (Table 1). No respondent reported providing cosmetic procedures (neurotoxins, lasers, and fillers); however, among surgical services, 50% reported performing biopsy and 40% reported performing excisions.

Commonly reported challenges included lack of space (n = 6), financial restrictions (n = 5), and poor access to equipment (n = 5). Qualitative facilitators included institutional support, clinic scheduling, teledermatology, and medication access. Qualitative barriers included security concerns, lack of specialty care, patient transportation, limited access to medication, inter-facility interoperability, no-show rates, and scheduling. Nine of the 10 respondents noted teledermatology as a potential or proven positive adjunct to traditional dermatologic care; however, limited infrastructure (technology, providers, and software) precludes broad implementation. Modes of care included in-person clinics at a main hospital with patients transported from prison, a designated secured clinical setting, store-and-forward e-consults, and live interactive teledermatology. One model operated with one half-day in-person clinic per week (for 30 patients) and a separate half-day dedicated to procedures (excisions and slow Mohs surgery). In addition, telemedicine clinics occurred twice a month (for 10 patients).

COMMENTS

Incarcerated patients are at a higher risk of acquiring many disease conditions, with a high prevalence of dermatologic pathologies.[3] Our cohort reported impediments to care delivery, such as security concerns, transportation, population transience, and discontinuity in electronic medical record (EMR) between facilities. Unique dermatologic challenges reported by our cohort included a limited formulary at certain facilities and facility restrictions on medications in living care homes; however, supplies and policies can vary. Notably, one respondent reported no challenges,and another reported robust access to advanced therapeutics. As a result, significant disparities could exist in access to dermatologic care between facilities. Financial restrictions were also cited as a significant barrier with downstream effects, including lack of space and appropriate equipment. Modern dermatologic practice includes both medical and procedural/surgical components. Certain correctional dermatology clinics of the cohort surveyed may be more robust in medical elements versus those of surgery; this may affect the prevalence and treatment of specific disease conditions across facilities.

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Table 1. Noted Barriers, Facilitators, Challenges, and Demographics of Care in a Correctional Dermatology Setting.

Challenges	Count (%)
Lack of space	60 (n = 6)
Financial restrictions	50 (n = 5)
Poor access to equipment	50 (n = 5)
Lack of institutional support because of legal or regulatory reasons	20 (n = 2)
Unclear patient needs	20 (n = 2)
Qualitative facilitators	
Institutional support (e.g., clinic infrastructure)	30 (n = 3)
Clinic scheduling (e.g., consistent schedule to promote adherence)	20 (n = 2)
Teledermatology	30 (n = 3)
Access to medications (e.g., access to advanced therapeutics)	20 (n = 2)
Qualitative barriers	
Security	30 (n = 3)
Lack of speciality care	20 (n=2)
Transportation of patients	30 (n = 3)
Limited medication access (e.g., limited formulary)	30 (n = 3)
Limited communication (e.g., between correctional facilities) and records transfer (e.g., interoperability)	20 (n = 2)
No-show rate (e.g., 35%–50%)	20 (n = 2)
Scheduling	20 (n = 2)
Conditions observed	Infections (condyloma, fungal infections, scabies, syphilis, tinea, venereal warts, and warts), autoimmune (psoriasis), cancer (neoplasms of concern, skin cancer/actinic keratosis), dermatitis (eczematous dermatitis, seborrheic dermatitis, severe atopic dermatitis, and stasis dermatitis), hair disorders (acne keloidalis nuchae, folliculitis, folliculitis decalvans, and pseudofolliculitis barbae), other conditions (acne, hidradenitis suppurativa, keloid, and venous ulcers)
Common procedures	
Skin biopsy	50% (n = 5)
Excision (benign or malignant)	40% (n = 4)
Intralesional injections	20% (n = 2)
Cryotherapy	20% (n = 2)
Mohs surgery	10% (n = 1)
None	30% (n = 3)
Clinic format	
In-person only	50 (n = 5)
Hybrid in-person with teledermatology	50 (n = 5)
Monthly operating hours	
1–10	40 (n = 4)
10–99	50 (n = 5)
>100	10 (n = 1)
Monthly patients examined	
1–10	10 (n = 1)
11–20	50 (n = 5)
>30	40 (n = 4)
Years of practice	
>6	100 (n = 10)
Clinic staff	
Attending and residents	80 (n = 8)
Attending only	20 (n = 2)

Telemedicine in the past was employed in correctional settings to improve access to care.[4,5] Our cohort endorsed dermatologic telemedicine as a means of triage and follow-up but not as a substitute for in-person treatment. Lack of regular patient access to the patient portal, poor audiovisual equipment, and limited infrastructure were the most cited impediments to implementation.

CONCLUSIONS

Our study combines the experiences of dermatologists involved in the care of incarcerated patients. Limitations of this study included convenience sampling by way of limited access to correctional dermatologists. Future studies should identify best practices, new implementations, and policy levers to address the highlighted facilitators and barriers.

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Short-Term Combination Treatment with Urea 50% and Calcipotriene/Betamethasone Dipropionate Aerosol Foam in Nail Psoriasis

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To the Editor:

Nail psoriasis affects 80%–90% of patients with psoriatic disease and is more prevalent with psoriatic arthritis.[1] Topical therapy is generally the treatment of choice in patients with mild/few nail disease the obvious advantage of avoiding adverse events of systemic treatment. Vitamin D analogs and steroids as creams and ointments, or calcipotriene/betamethasone dipropionate (Cal/BD) foam, have been documented as effective topical therapy.[2] Clinical lessening with topical agents is expected in 3–6 months, or it may take a year or longer to reach the complete lessening of the condition.[3] In patients with prominent subungual hyperkeratosis, treatment response is delayed or even remains unobserved.

OUR PATIENTS

We present three patients with nail psoriasis, successfully treated with a combination therapy of Cal/BD foam and anhydrous urea paste 50% (Relife U-Life™, Italy) for three months, with an intensive treatment regimen, accompanied by 1-year maintenance therapy. All patients provided written informed consent for publishing of images.

1. The first patient was a 58-year-old Caucasian woman with nail psoriasis on the left big toenail as demonstrated in Figure 1A, with a target (worst) Nail Psoriasis Severity Index (NAPSI) score of 10, accompanied by mild plaque psoriasis on the trunk with Psoriasis Severity Index (PASI)

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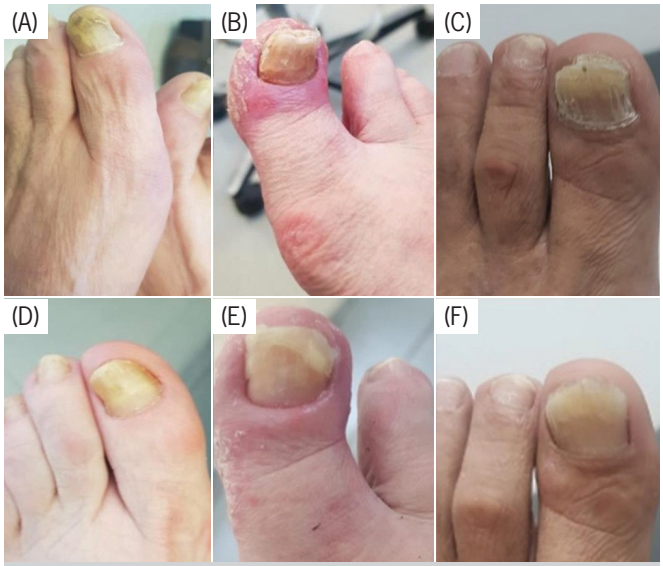

Figure 1. (A) Patient 1: nail psoriasis with onycholysis and hyperkeratosis of nail bed of the left big toenail; (B) Patient 2: nail psoriasis with hyperkeratosis of the nail bed and inflammation in the periungual region; (C) Patient 3: nail psoriasis with hyperkeratosis of the left big toenail; (D) First patient 3 months following the treatment; (E) Second patient 3 months following the treatment; (F) Third patient 3 months following the treatment.

score of 5. The patient was under medication for arterial hypertension.

2. The second patient was a 54-year-old Caucasian woman with nail psoriasis on the right big toenail and inflammation in the periungual region (Figure 1B), with a target NAPSI score of 8 accompanied by scalp psoriasis and an etymology of systemic diseases.
3. The third patient was a 62-year-old Caucasian man with nail psoriasis on the left big toenail (Figure 1C), with a target NAPSI score of 8 and moderate plaque psoriasis on the legs with a PASI score of 4. This patient was treated for arterial hypertension, coronary disease, and diabetes mellitus.

RESULTS

All the patients were treated with Cal/BD foam every morning and anhydrous paste of urea 50% every night under occlusion for three months, with a maintenance therapy twice-weekly for a year. Each of the patients demonstrated lessening and almost clearance of nail psoriasis within three months, with target NAPSI scores 4, 4, and 2, respectively (Figures 1D–1F). Remission was sustained with maintenance therapy for a year, without adverse events.

COMMENTS

Nail psoriasis has a significant impact on the quality of life of patients. Topical treatment is challenging and time-consuming. Prolonged application is required due to limited penetration through the psoriatic nail plate, leading to poor patient adherence.[4]

Adding once-daily topical application of urea 50% to Cal/BD foam resulted in rapid lessening of the condition, long-term control of the disorder, and better patient compliance. Although a double-blind study evaluating hyperkeratosis thickness in patients with severe subungual hyperkeratosis would be needed to establish reduced treatment duration with the addition of topical urea 50%, the results presented are encouraging. Once-daily use of the regimen for three months, continuing with twice-weekly application for a year resulted in nail thinning and regression of hyperkeratosis in the reported patients. In addition, we did not observe adverse events, such as nail avulsion, with the therapy.

Urea at a concentration of 30%–50% is used to reduce thickening of the nails. If this is applied under occlusion, lessening is even more rapid. In addition, urea enhances absorption of other drugs in the area of application. The mechanism of action is through gradual disintegration of the corneocytes that starts in the superficial layers and extends to the deeper nail plate structures. Lessening of nail psoriasis using various concentrations of urea has been reported as well.[5]

CONCLUSIONS

A combination of urea, vitamin D analogs, and topical steroids offers a better and more affordable safety profile for lessening nail psoriasis.

CONFLICT OF INTEREST

Dr. Tampouratzi reports research support and/or consultant and/or lecturer for AbbVie, LEO Pharma, Janssen, Sanofi, Genesis Pharma, UCB, Mylan and Novartis, outside the submitted work. Dr. Sfaelos is an employee of LEO Pharma. Dr. Rigopoulos reports research support and/or consultant and/or lecturer for Abbvie, Genesis Pharma, Janssen, LEO Pharma, Sanofi and Novartis outside the submitted work. Pesiridis is an employee of LEO Pharma. Drs. Kostaki and Gregoriou reported no conflict of interest with any financial organization regarding the material discussed in the manuscript. Dr. Micali received honoria from Abbvie, Almirall, Alfasigma, Amgen, Biogen, Janssen, Leo Pharma, Eli Lilly, Novartis, Pfizer, Sandoz, and UCB.

AUTHOR CONTRIBUTIONS

All authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship. The authors were responsible for all aspects of manuscript development and had made substantial contributions to research and collection of data. All authors contributed equally, and read and approved the final version of the manuscript.

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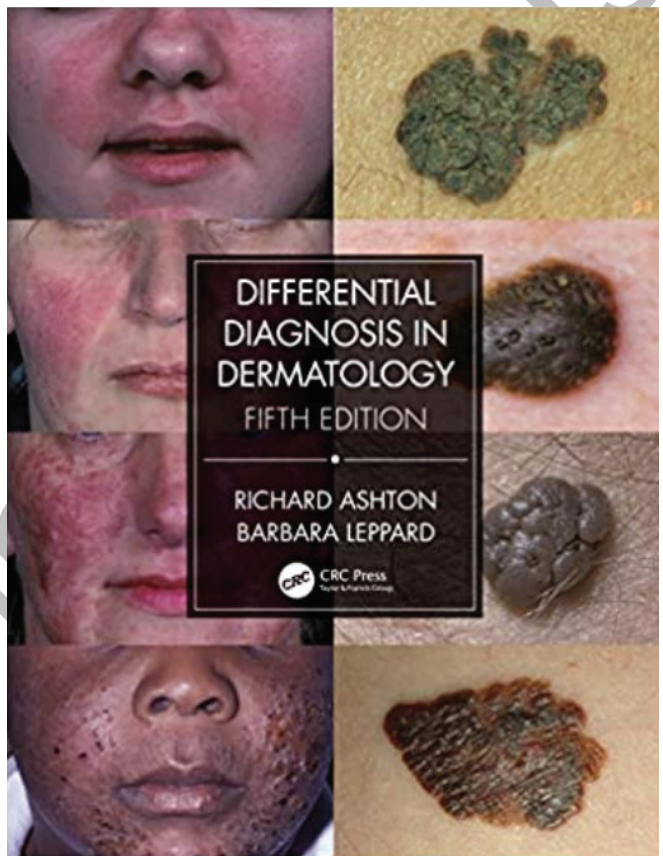
VINTAGE LABEL

BOOK REVIEW

Jennifer L. Parish, MD, Section Editor

Differential Diagnosis in Dermatology

R Ashton, B Leppard. *Differential Diagnosis in Dermatology*, Fifth Edition. CRC Press, London; 2021; 358 pages, $54.95. eBook ISBN: 9780429023248



The fifth edition of Differential Diagnosis in Dermatology expands upon an already fantastic resource for diagnosing and treating common skin conditions. As the cover of the book suggests, this text includes many images. Subsequent to the first edition that was published in 1989, the authors have continued to excel in showcasing numerous detailed clinical images of cutaneous diseases in patients with various skin types. Alongside the images are concise but thorough reviews of the conditions and appropriate up-to-date treatment options. This book is full of high-yield pictures and information, making it well-suited for practicing dermatologists, medical students, residents, and generalists.

The book begins with an introduction to diagnosing dermatologic conditions. This section includes a step-by-step process of appropriately describing skin lesions (with the help of corresponding clinical images). The first chapter ends with a brief review of dermatoscopy of common cutaneous lesions encountered in dermatology and illustrates the essential features that can differentiate benign from malignant lesions. The second chapter consists of a concise review of pharmacology in dermatology, including but not limited to wound care, topical treatments, oral antimicrobials, immunosuppressives, and light therapy.

The remainder of the book includes 12 chapters covering common conditions based on location (genitalia, legs, etc.). The unique layout of each chapter allows physicians to reference quickly the text, building a differential diagnosis even in the clinic. For example, suppose a patient presents with dermatitis localized to the hands and feet. The reader could go to the corresponding chapter to assist in building a differential diagnosis and treatment plan for the patient, because the same condition may present at different locations (dermatophytosis, for example). The physician can review these conditions for multiple times and observe how the morphology may differ depending on the anatomic location. The text also includes many clinical images of how conditions present in patients with skin of color, outlining the importance of becoming familiar with the differing morphology. There are also illustrations outlining key concepts and tables that provide an algorithmic approach to diagnosis and/or treatment, thus allowing for a pleasant reading experience.

The strength of this book is the amount of concise practical information contained in it while also being comprehensive. Every chapter provides countless clinical images and a brief review of the conditions, making every page high-yielding and easy to read. This book is appropriate not only for learners interested in dermatology but also for all physicians who come across patients with cutaneous diseases.

Reviewed by Jordan Hyde, MD, Department of Dermatology, Temple University Lewis Katz School of Medicine, 3401 N, Broad Street, Philadelphia PA 19140 • E-mail: Jordan.Hyde@tuhs.temple.edu

IMPORTANT INFORMATION ABOUT

VTAMA® (Vee-TAM-uh)
(tapinarof) cream, 1%

BRIEF SUMMARY

This summary contains important information about VTAMA cream. It is not meant to take the place of your doctor's instructions. Read this information carefully before you start using VTAMA cream. Ask your doctor or pharmacist if you do not understand any of this information or if you want to know more about VTAMA cream. For full Prescribing Information and Patient Information, please see the package insert.

WHAT IS VTAMA cream?

VTAMA cream is a prescription medicine used on the skin (topical) to treat plaque psoriasis in adults. It is not known if VTAMA cream is safe and effective in children under 18 years of age.

Do not use VTAMA cream for a condition for which it was not prescribed. Do not give VTAMA cream to other people, even if they have the same symptoms you have. It may harm them.

Important: VTAMA cream is for use on the skin (topical use) only. Do not use VTAMA cream in your eyes, mouth, or vagina.

WHAT SHOULD I TELL MY DOCTOR BEFORE USING VTAMA cream?

Before you use VTAMA cream tell your doctor about all of your medical conditions, including if you:

- Are pregnant or plan to become pregnant. It is not known if VTAMA cream will harm your unborn baby; and/or
- Are breastfeeding or plan to breastfeed. It is not known if VTAMA cream passes into your breast milk. Talk to your doctor about the best way to feed your baby during treatment with VTAMA cream.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

HOW SHOULD I USE VTAMA cream?

- Use VTAMA cream exactly as your doctor tells you to use it.
- Apply a thin layer of VTAMA cream only to your psoriasis skin lesions one (1) time a day. Avoid applying VTAMA cream to unaffected areas of your skin.
- Wash your hands after application, unless VTAMA cream is for treatment of your hands.
- If someone else applies VTAMA cream for you, they should wash their hands after application.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF VTAMA cream?

The most common side effects include: folliculitis (red raised bumps around the hair pores), nasopharyngitis (pain or swelling in the nose and throat), contact dermatitis (skin rash or irritation, including itching and redness, peeling, burning, or stinging), headache, pruritus (itching), and influenza (flu).

These are not all the possible side effects of VTAMA cream. Call your doctor for medical advice about side effects.

You are encouraged to report negative side effects of prescription drugs to the FDA at www.fda.gov/medwatch or call 1-800-FDA-1088.

HOW SHOULD I STORE VTAMA cream?

- Store VTAMA cream at room temperature, between 68°F to 77°F (20°C to 25°C).
- Do not freeze VTAMA cream.
- Protect VTAMA cream from exposure to excessive heat.
- Keep VTAMA cream and all medicines out of the reach of children.

WHAT ARE THE INGREDIENTS IN VTAMA cream?

Active ingredient: tapinarof

Inactive ingredients: benzoic acid, butylated hydroxytoluene, citric acid monohydrate, diethylene glycol monoethyl ether, edetate disodium, emulsifying wax, medium-chain triglycerides, polyoxyl 2 stearyl ether, polyoxyl 20 stearyl ether, polysorbate 80, propylene glycol, purified water, and sodium citrate dihydrate.

Dermavant Sciences Inc., Long Beach, CA 90806 USA

dermavant®

VTAMA®
(tapinarof) cream 1%

Now FDA Approved

VTAMA cream can give plaque psoriasis patients significantly clearer skin.

So they're free to think about...**literally anything.**

VTAMA cream is a once-daily, non-steroidal topical for adults with plaque psoriasis.[1,2]

- 36% and 40% Physician Global Assessment (PGA) success rate* in two 12-week pivotal studies vs 6% and 6% for vehicle[2]
- Safe and well-tolerated even on the face, neck, intertriginous areas, inframammary areas, axillae, genitalia, and anal crux.[1,3,4]
- A median ~4 month off-treatment effect seen in long-term, open-label extension study of patients (n=73)[2]

See the data: **VTAMA.com**

*PGA success rate defined as PGA=0 or 1 and ≥2-grade improvement from baseline at week 12.

Important Safety Information: Indication: VTAMA® (tapinarof) cream, 1% is an aryl hydrocarbon receptor agonist indicated for the topical treatment of plaque psoriasis in adults. **Adverse Events:** The most common adverse reactions (incidence ≥1%) in subjects treated with VTAMA cream were folliculitis (red raised bumps around the hair pores), nasopharyngitis (pain or swelling in the nose and throat), contact dermatitis (skin rash or irritation, including itching and redness, peeling, burning, or stinging), headache, pruritus (itching), and influenza (flu).

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call **1-800-FDA-1088**.

References: 1. Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 trials of tapinarof cream for plaque psoriasis. *N Engl J Med.* 2021;385:2219–2229. **2.** VTAMA (tapinarof) cream, 1%. Prescribing Information. Dermavant; 2022. **3.** Strober B, Stein Gold L, Bissonnette R, et al. Tapinarof cream 1% once daily for plaque psoriasis: long-term extension trial of a novel therapeutic aryl hydrocarbon receptor modulating agent. Oral presentation at European Academy of Dermatology and Venereology; September 30, 2021. **4.** Stein Gold L, Kircik L, Lebwohl M, et al. Tapinarof cream 1% once daily for plaque psoriasis: favorable local tolerability in two pivotal phase 3 trials. Poster presentation at Innovations in Dermatology 2021; March 16–20, 2021.

Please see the Brief Summary of VTAMA cream on the following page.

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