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September/October 2019 Volume 17 Issue 5

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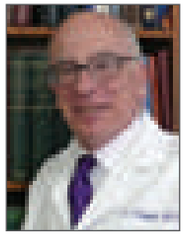
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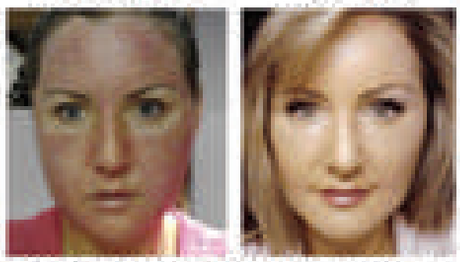
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EDITORIAL

Dermatologic Manifestations of the 1918–1919 Influenza Pandemic

Jordan V. Wang, MD, MBE, MBA,[1] Lawrence Charles Parish, MD, MD (Hon)[1,2]

The 1918–1919 influenza pandemic, commonly known as the Spanish flu, was an unusually deadly outbreak that infected about one-third of the world's population at the time or about 500 million people worldwide.[1] Total deaths from the epidemic exceeded those killed in the Great War (World War I) and were estimated to be about 50 million but may have been upward of 100 million by some accounts. For years, it was postulated by many that the culprit virus, being novel H1N1 viruses, was extraordinarily aggressive and led to a secondary bacterial pneumonia that proved fatal for the vast majority of patients;[2] however, more recent theories point to the fact that malnutrition, poor hygiene, meager living conditions, and overcrowded medical facilities played a major role. With such high death rates and very little concrete evidence, much remains a mystery about this particular influenza pandemic. Of interest to this presentation are the dermatologic manifestations in those who had fell victim.

CLINICAL AND PATHOLOGIC PRESENTATION

In an account published in *The Lancet* in 1918, discussions at the Royal Society of Medicine in London described the postmortem and clinical findings of patients.[3] A common theme that was observed included significant and profound inflammation of the airways, which was often associated with purulent exudates, abscess formation, and acute hemorrhage. Clinical cases were described by Captain C. F. Graham of the United States Marine Corps as being characterized by "intense cyanosis, frequent jaundice, high fever, and extreme prostration." Illustrative reports described a "distinctive posture, breathing quickly, and of a blue colour approaching heliotrope, but there is no true dyspnea ... there may be purpuric patches and perhaps subcutaneous emphysema." The subcutaneous emphysema was typically seen "commencing in the neck and spreading downwards..."[3] Skin manifestations are reported as being distinct and frequent in those who were affected.

Another report in *The Lancet* at that time described the skin as being "hot, dry, and pungent as in lobar pneumonia, occasionally a scarlatiniform rash of transient duration may develop."[4] Alternatively, the skin could also be "covered with profuse clammy sweat ... often leading to sweat vesicles." This account continues to describe the "facies is at first flushed and red, but in bad cases it speedily becomes less and less of a purely red tint and assumes more and more of a lavender, heliotrope, or violaceous hue." Several victims were also reported to have painful edema of the feet that included "diffuse dull red deep-seated purpuric tender spots," which were compared to "those described by Osler in cases of infective endocarditis" and thought to be due to local thrombotic or embolic changes. A few cases of *Herpes simplex* infection on the face and ears were also reported, but they were rarely extensive. Another report estimated the frequency of herpes on the face and lips to be about 10% of cases.[5]

An account of the epidemic among American troops in England also detailed the characteristic "early developing and profound cyanosis seen in all the severer cases," which was described as a "peculiar tint, a deep lavender or heliotrope."[6] The American army physicians reported that no cause could be found in the circulation of the patients. They found no consistent dilatation of the right heart, pulse of poor quality, or low blood pressure that could represent a potential cause. Cases of subcutaneous emphysema of the neck and upper portions of the chest were similarly observed. In addition, 15 cases presented with "swollen, painful feet, and several of these showed acute red inflammatory areas over the toes and instep..."[6] These authors found their observations to be "similar to those described by Osler in malignant endocarditis."

From the Department of Dermatology and Cutaneous Biology,[1,2] and Jefferson Center for International Dermatology,[2] Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA

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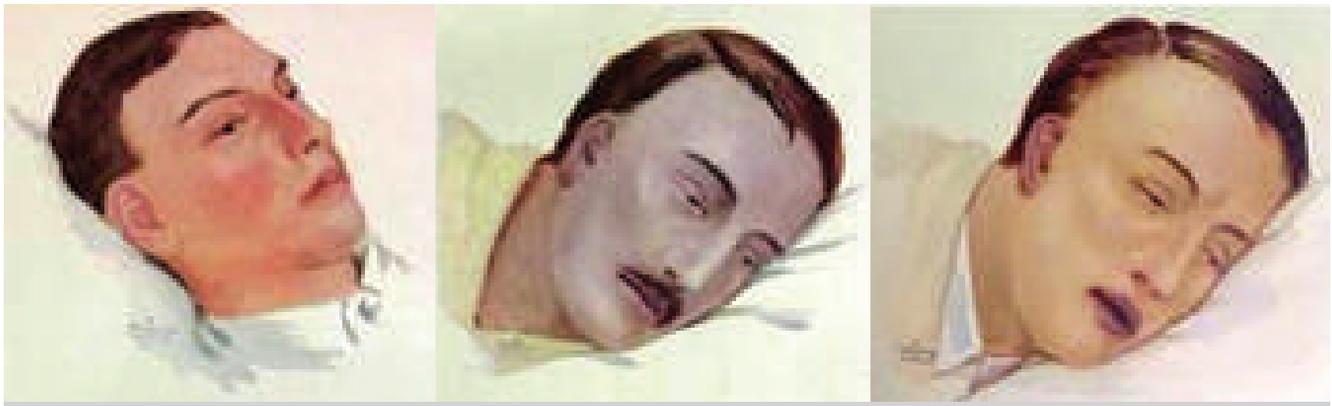


Figure 1. Cyanosis associated with influenza, drawn by W. Thorton Shiells, London, England. Originally published in Abrahams et al.[4]

This distinctive blue cyanotic skin was so profound that it became known as "heliotrope cyanosis."[2–4,7] This was believed to be "an evil sign, for few cases recover when once this characteristic hue has been established."[4] Physicians at the time even went so far as to note that "so long as his lip and ear colour, whatever its degree, is *red* there is ample room for hope and recovery, no matter what the lung signs, the temperature, the pulse rate, or the respiration rate."[4] In the absence of any other worrisome, dangerous, or ominous signs, the heliotrope color—even if confined to just the lips or ears—could help "pick out those cases in a ward that are likely to be dead in a day or two." Unfortunately, it seems as if the cause of this cyanosis remains a mystery. A theory put forth by Charles F. Hoover (1865–1927), a distinguished physician from Cleveland, Ohio, was mentioned, which postulated that the significant "presence of foam in the bronchial tree will cause a marked hindrance to gas exchange";[6,8] however, in contrast, various reports had mentioned that a characteristic feature of the cyanosis was the complete absence of both subjective distress and air hunger.[3,5]

CONCLUSIONS

What can be universally agreed upon about the 1918–1919 influenza pandemic is that it was a tragic and deadly outbreak with three successive waves in less than a year. Curiously, the Spanish flu continues to be shrouded in mystery as much remains unknown. Not only did it have unique epidemiologic patterns, but it also had remarkable symptomatology, including unique dermatologic manifestations. The heliotrope cyanosis stands out to define this period of medicine, especially as the British Army Medical Corps had to bring in W. Thorton Shiells, an artist from the Royal Academy of Art in London, to capture the distinct color for their publication.[4]

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ORIGINAL CONTRIBUTION

Efficacy of an Innovative Film-Forming Wound Dressing on Open Wounds

Xavier Cubiró Raventós, MD;[1] Víctor-Adrian Flores Climente, MD;[1] Xavier García Navarro, MD;[2] Amalia Perez Gil, MD;[3] Rafael Salido Vallejo, PhD;[4] Francisco Javier Vázquez Doval, PhD[5]

ABSTRACT

Standards in post-surgery wound care management require a rapid healing process in order to prevent and minimize abnormal scarring. For the healing process to start as early as possible, the ideal dressing should be applied directly on the open wound and perfectly adapt to it. The authors report a case study series regarding the efficacy of a flexible film-forming wound dressing in the form of a gel (Stratamed®, Stratpharma AG, Switzerland) that is approved for the use on open wounds and injured skin. Evidence from the current study shows that, while remaining safe to use, the dressing was efficacious in promoting epithelialization and accelerated wound healing of areas in which skin integrity had been compromised, and at the same time prevented the formation of abnormal scars. Results were observed across a broad range of dermatologic surgical procedures. All treated conditions showed a beneficial outcome, as well as an overall favorable patient treatment perception. (*SKINmed*. 2019;17:298–304)

INTRODUCTION

Wound care management aims at reestablishing skin functions in a timely manner, avoiding risks of infection, and controlling inflammation signs connected to the epidermal barrier disruption. The ideal scarring process entails acceptable scar maturation concurrently to the avoidance of abnormal scarring.[1]

Moist wound healing is a fundamental aspect to take into account when preventing abnormal scarring and at the same time improving healing time. It promotes fast tissue reepithelialization and prevents scab formation.[2]

A suitable full-contact device consisting of a self-drying, film-forming wound dressing in a gel format (Stratamed®, Stratpharma AG, Switzerland) has been demonstrated to prevent transepidermal and dermal water loss, providing adequate hydration and creating the ideal conditions for an efficient reepithelialization.[3] The following cases reflect further evidence of the efficacy of this device in several indications.

Case 1: Treatment of scalp defect after cutaneous tumor removal

Cutaneous squamous cell carcinoma (CSCC) is a malignant and infiltrating tumor with disseminating properties. The majority of these tumors emerge in photoexposed areas, such as the patient's head and neck region. Conventional surgery is the primary therapeutic option, allowing in most cases tumor eradication and immediate reconstruction through direct closure, skin grafts, or flaps.[4]

Full-thickness skin grafts represent a valid scalp reconstruction alternative when the defect is extended or when it is preferable to avoid the displacement of large flaps, such as in patients of advanced age.

A 78-year-old man without relevant pathologic history or known drug allergies was diagnosed with a CSCC on a hairless area of the scalp. The patient reported occupational solar chronic exposure. Physical examination revealed multiple lentigos and actinic keratoses in the photoexposed skin areas. The patient presented with a 5-cm lesion with a hyperkeratotic scab, which had evolved over

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the previous 5 months, with a particularly rapid growth in the last 20 days (Figure 1a).

Surgical excision of the lesion was performed under local anesthesia, and the skin defect was closed with a supraclavicular full-thickness skin graft. Nine days post-surgery, total necrosis of the skin graft occurred (Figure 1b).

After topical enzymatic debridement of the necrotic tissue, a 6-cm diameter skin defect was left, affecting the entire dermo-epidermal thickness and exposing a 12-mm periosteum area (Figure 1c).

A 48-hour wound management protocol was established, alternating topical antimicrobials and the studied wound dressing. In each management cycle, wound bed cleansing and light manual debridement of the borders were performed, together with application of one of the two topical products under a secondary physical dressing.

Six weeks after protocol establishment, the skin defect had diminished. The area with exposed periosteum had healed, and granulation of the wound bed and epithelialization of the borders occurred, leading to a 15-mm reduction in the defect dimensions (Figure 1d).

The 48-hour wound management protocol was then modified by replacing topical antimicrobials with local antiseptics. After 3 months, the wound gave an acceptable appearance. The skin defect completely healed completely 6 months after the treatment, with an excellent cosmetic outcome (Figure 1e).

The current case represents reliable evidence in treating a wound closure by secondary intention with the full-contact wound dressing, therefore avoiding additional surgery baring well-known risks in patients of advanced age, in a highly vascularized area with a high bleeding risk.

From the first moments of wound management with the film-forming dressing, the evolution of the wound appeared extraordinarily favorable, without adverse events, either local or systemic complications. The full-contact wound dressing maintained a moist wound bed environment and promoted granulation and epithelialization of the skin, achieving an excellent aesthetic outcome.

Case 2: Management of open wound caused by second-degree burn

A 75-year-old woman sustained a 5 cm × 4 cm uninfected second-degree burn on the right breast (Figure 2a). Following treatment with topical silver sufadiazine for seven days, the film-forming wound dressing was applied twice daily. After 11 days of treatment with the wound dressing, the open wound size was greatly reduced (Figure 2b). After 36 days following the start of treatment with the wound dressing, complete epithelialization occurred, with only a slight residual erythema (Figure 2c).

The use of the innovative film-forming wound dressing decreased the existing inflammation as well as the pain perceived by the patient, improving skin elasticity and preventing hypertrophic or keloid scarring, together with an enhanced aesthetic final result.

This dressing can be considered an efficacious treatment option in case of skin burns without excessive discharge, in order to accelerate epithelialization and improve the aesthetic outcome.

Case 3: Film-forming wound dressing post CO_2 laser treatment

A 74-year-old man without previous relevant morbidity consulted for multiple superficial lesions characterized by redness and desquamation in different areas of the face and scalp (Figures 3a and 3b).

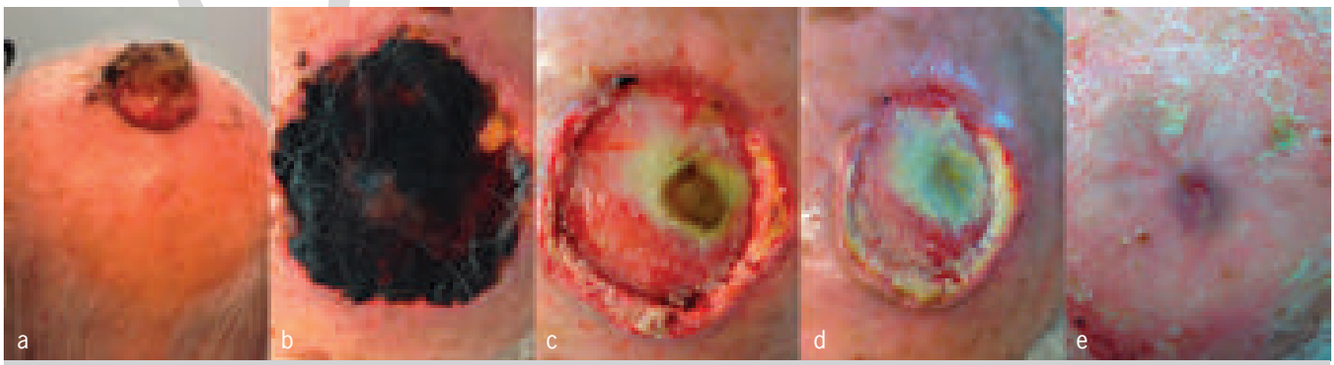


Figure 1. (a) A dome-shaped lesion with a hyperkeratotic crust (b) post-surgery necrotic skin graft, (c) debridement of necrotic skin graft, (d) 6-week treatment with film-forming wound dressing and topical antibiotic, and (e) 6-month treatment with film-forming wound dressing and local antiseptics.

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Figure 2. (a) Second-degree burn wound, (b) wound evolution 11 days after using the film-forming wound dressing, and (c) wound evolution 36 days after treatment with film-forming wound dressing.



Figure 3. (a and b) Superficial actinic keratoses, (c) patient after CO_2 laser therapy, prior to treatment with film-forming wound dressing, and (d and e) wounds evolution 13 days after using the film-forming wound dressing.

He had worked outside for many years and had developed significant sun damage. A clinical diagnosis of actinic keratoses was made.

The patient was treated with CO_2 laser, following which he was to apply the wound dressing several times daily (Figure 3c).

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Results 13 days post-treatment are shown in Figures 3d and 3e.

Precancer cutaneous lesions are very common among the Caucasian population. Although the probability of malignant transformation into CSCC is relatively low, such lesions require treatment. In the current patient, a CO_2 laser treatment was carried out on the lesions, eliminating the most superficial layers of the epidermis and reaching the dermis. To enhance the healing process, the wound dressing was applied, allowing reduction of erythema, diminished pruritus, and avoidance of post-op infections, together with an overall positive patient treatment perception.[5]

Case 4: Simple advancement pedicle flap of the pterion

A 76-year-old man without known drug allergies and with a history of type II diabetes, essential arterial hypertension, and acute myocardial infarction presented with a cutaneous tumor in the right pterion on the site of a previous seborrheic keratosis excision. It had significantly enlarged during the past 3 months. Physical examination revealed a 3-cm diameter keratotic tumor, presenting with a central scab and signs of dermatoscopy-confirmed irregular vessels. Punch biopsy of the lesion revealed a keratinizing cSCC. The diagnosis of a squamous cell carcinoma was confirmed histologically.

The lesion was excised under local anesthesia and posterior reconstruction of the cutaneous deficit was carried out through a simple advancement pedicle flap (Figure 4a), after which the wound dressing was applied.

In Figure 4b, it is possible to observe the positive evolution of the lesion 2 months post-surgery, with a favorable aesthetic outcome, with feebly erythematous margins, and with and no inflammatory signs.

CSCC is the second most frequent type of cutaneous neoplasia, and its incidence has increased considerably over the past 20 years. Most CSCCs are localized and usually removed through surgical excision. A subgroup of CSCC exists that shows a high tendency to relapse, with lymphatic dissemination and invasion of distant organs.[6,7]

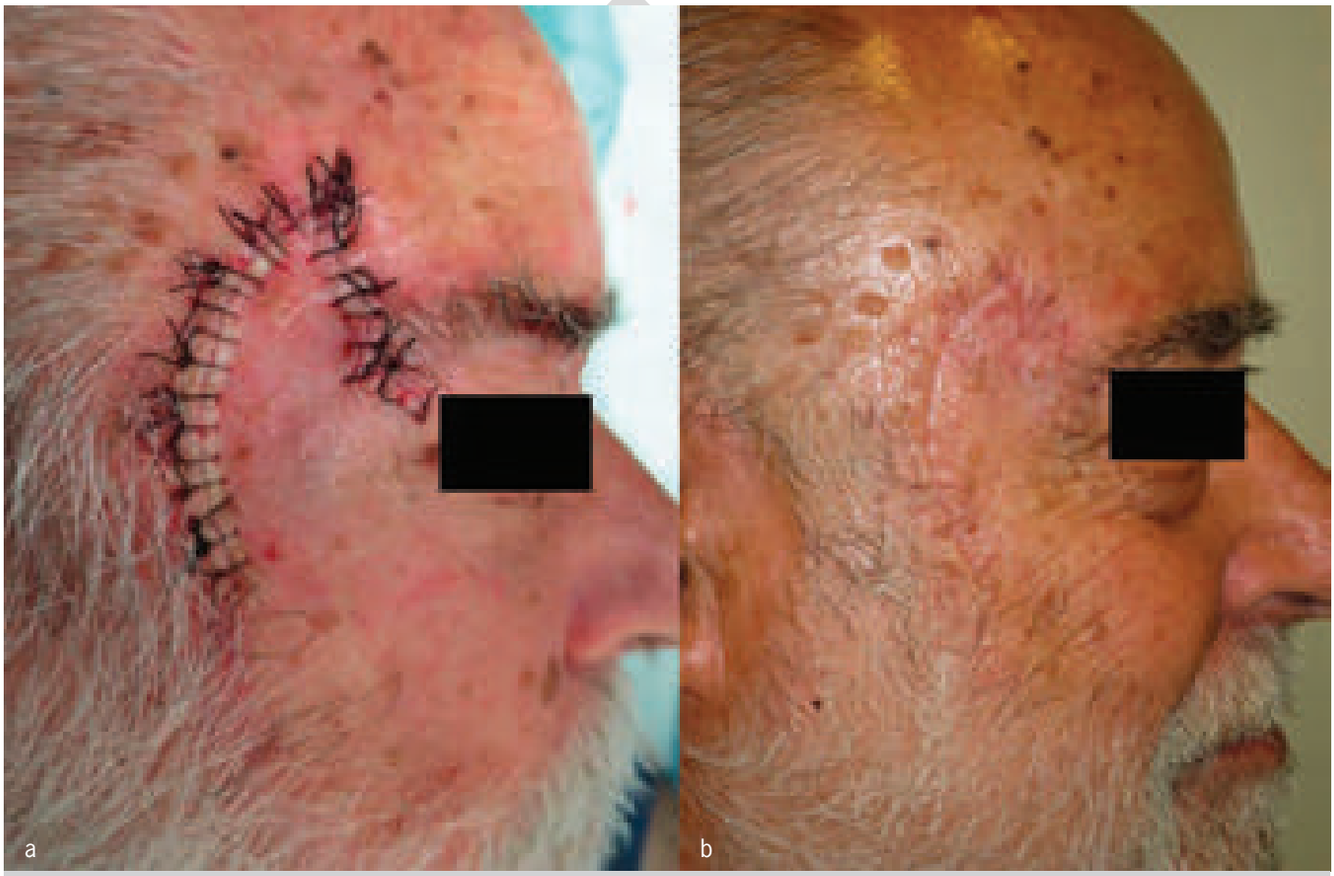


Figure 4. (a) Tumor excision and simple flap reconstruction immediately after surgery and (b) wound evolution 2 months after surgery.

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Although several treatments are available for this type of cutaneous cancer, complete surgical excision with free histologic margins of neoplasia remains the best available option. Once the tumor is eradicated, all efforts should be directed towards preventing cutaneous defects. For this purpose, in order to reduce inflammation and avoid risks of infection, an inert and bacteriostatic full-contact wound dressing can be the most suited solution. The implemented wound dressing is a topical, transparent, and self-drying gel that ensures full contact with the affected surface, creating an optimal moist wound environment, yet avoiding maceration due to its gas permeable nature.

The dressing protected the wound from microbial and chemical invasion, promoting the formation of a mature scar with a low inflammatory degree. It enabled excellent aesthetic results, without signs of inflammation during the healing process and the absence of hypertrophic scars.

Case 5: Basal cell carcinoma excision

A 90-year-old man without known drug allergies, with type II diabetes and essential arterial hypertension, presented with a lesion on the left temple. The tumor had been previously treated with cryotherapy (without resolution) and had been progressively growing for 4 months, reaching a diameter of 7 mm. Dermatoscopy examination suggested a diagnosis of basal cell carcinoma (BCC), which was subsequently confirmed by punch biopsy (Figure 5a).

The lesion was surgically excised. Wound closure was performed with subcutaneous and dermis suture. A thin layer of wound dressing was applied every 12 hours for 14 days on the affected area.

Ten days post-surgery, the sutures were removed. It was possible to observe a satisfying wound appearance with a correct scarring process (Figure 5b). Neither signs of infection nor surgical dehiscence areas were observed. Only mild erythema (which is common after such a procedure) was present, which was no longer visible 1 month post-surgery (Figure 5c).

The main considerations from the described case focus mainly on the cosmetic results achieved a few days post-surgery and the absence of inflammatory and infectious signs obtained through the application of the studied wound dressing twice daily during 14 days.

This innovative dressing is a topical device indicated for post-surgery procedures. One of the critical aspects concerning the correct use of the studied dressing is that unlike other commercialized topical products, treatment can start immediately after surgery, prior to scar formation. The relevance of this feature lies in the markedly improved scarring process, especially avoiding abnormal scarring.[5] The dressing enabled this process in a fast manner, generating positive cosmetic results.

Other favorable elements to consider are the excellent safety of the product and the patient-perceived ease of use, factors that make the dressing a highly recommended product for dermatologic post-surgery care.

Case 6: Treatment of severe cutaneous reactions induced by topical imiquimod

Iatrogenic reactions are common in clinical practice; in the cutaneous oncology area, a number of topical therapies are available for treating actinic keratoses, which can produce different levels of inflammatory response. This can lead to therapy interruption, with direct repercussions on the treatment outcome. The difficulties in predicting the degree of reactions, as well as intrinsic differences among patients, highlight the need for specific measures regarding the management of the inflammatory response.

An 82-year-old man previously treated for actinic keratoses with imiquimod 5% cream presented with an intense inflammatory



Figure 5. (a) Basal cell carcinoma excision immediately after surgery, (b) wound healing 10 days after surgery, and (c) wound healing 1 month after surgery.

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Figure 6. (a) Severe inflammatory response on the scalp following imiquimod 5% cream treatment, (b) evolution of the inflammation after 2 weeks and (c) after 3 months of treatment with film-forming wound dressing.

response on the scalp 2 weeks after treatment completion (Figure 6a). Examination of the lesion revealed erythematous plaques with crusting and ulcerations in several regions of the scalp. Crusting and ulceration were present.

The patient had completed a 4-week cycle with 3 weekly applications, causing a severe and painful inflammatory reaction, in addition to a 37.5°C fever. After 2 weeks of symptomatic treatment with paracetamol, the fever resolved; nevertheless, local inflammation on the scalp persisted.

Absorbent wound dressings were applied in order to eliminate the existing residual exudate. Subsequently, the use of the wound dressing was implemented. After 2 weeks of treatment the patient showed a major improvement, with epithelialization of all ulcerated areas and minimal superficial scabs (Figure 6b).

Full recovery occurred 3 months post-treatment initiation, without residual scarring, hyperpigmentation, or other complications derived from the inflammatory reaction emerged with the use of topical imiquimod (Figure 6c).

Implementation of topical therapies for the treatment of actinic keratoses is a widespread practice in dermatology. Efficacy of these therapies is well established, as well as the related local inflammatory response, which can be very intense to the point of a flu-like syndrome. The management of local reactions can be problematic.[8]

Local reactions can range from pruritus to pain, or even a burning sensation; moreover, morbidity arising in such cases is a not only physical but can also significantly affect the patients' quality of life, for instance, producing avoidant social behaviors, isolation, and depressive disorders.[9]

Superficial skin erosions and ulcerations emerging from local responses to topical treatments have a high probability of causing permanent sequelae. For these reasons, the ideal therapy consists of a product capable of accelerating the epithelialization process, preventing the occurrence of abnormal scars, avoiding potential complications, with bacteriostatic activity, and without causing any interference with the inflammatory response that can generate a decrease in treatment efficacy.

The implemented film-forming wound dressing is, therefore, an extremely valid treatment option, considering its bacteriostatic activity and proven prophylactic efficacy in preventing the occurrence of abnormal scarring.[10]

DISCUSSION

Evidence from the cases presented suggest that the implemented self-drying, film-forming wound dressing is an excellent option for faster postoperative wound reepithelialization, especially for patients undergoing dermatologic surgery, in whom potential abnormal scarring and infection risks exist.

Based on clinical experience, absence of inflammation-related symptoms (such as pain and pruritus), satisfactory post-surgery cosmetic results, avoidance of abnormal scarring, and competitive price represent the main strengths of this product.

Finally, patients treated with the film-forming wound dressing were satisfied with the good cosmetic results following the surgical procedures.

CONCLUSIONS

Timely wound treatment is a key factor in minimizing abnormal scar formation.[11] The flexible, full-contact nature of the gel

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allowed an immediate post-surgery application of the dressing in all treated conditions, translating into an accelerated wound healing process.

Although the usage of the implemented product has been previously reported, the authors present supporting evidence for the safety and efficacy of the dressing on open wounds and compromised skin.

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ORIGINAL CONTRIBUTION

Genital Involvement in Bullous Fixed Drug Eruption

Anissa Zaouak, MD; Ines Chabchoub, MD; Dorra Essid, MD; Selima Ben Jennet, MD; Houda Hammami, MD; Samy Fenniche, MD

ABSTRACT

Bullous fixed drug eruption (FDE) is a severe reaction due to drug intake and requires specific management in dermatology. The sites of predilection are the lips, trunk, genitalia, and perineal area. The aim of our study was to assess the features and outcomes of bullous FDE with genital involvement through a retrospective study of 18 years (2000–2017) conducted in the Dermatology Department of Habib Thameur Hospital. Ten patients were included in the study. The ratio of men to women was 6.4. The mean age of the patients was 46.3 years. The most frequently affected genital site in men was the glans penis. Nonsteroidal anti-inflammatory drugs were the most frequent drugs associated with genital bullous FDE, followed by paracetamol and trimethoprim-sulfamethoxazole. Residual hyperpigmentation of the genitals was not observed in our patients. Genital involvement in bullous FDE is more frequent in men. (*SKINmed*. 2019;17:306–309)

Fixed drug eruption (FDE) is a common cutaneous drug reaction characterized by recurrent circumscribed lesions at the same skin or mucosal site after every intake of the causative drug.[1,2] Bullous FDE is a severe variant of the FDE.[3] The lesions can appear on any part of the body; however, the sites of predilection are the lips, oral mucosa, trunk, perineal area, and genitalia.[1,4] Bullous FDE of the genitals may be easily misdiagnosed with other bullous dermatosis or sexually transmitted diseases.[5] The aim of this study was to assess the epidemiologic, clinical, therapeutic, and evolving features of bullous FDE with genital involvement.

METHODS

We undertook a retrospective study of 56 cases of FDE recorded in the Dermatology Department of Habib Thameur Hospital between 2000 and 2017. We found 18 patients afflicted with bullous FDE. Among them, only 10 cases with genital involvement were included in the study. Data retrieved included age, gender, distribution, morphology, drugs involved, pharmacovigilance investigation, patch testing conclusions, histopathologic and direct immunofluorescence findings, response to therapy, and outcome.

RESULTS

Among the 10 patients, men predominated with a male/female sex ratio of 6.4. The age of the patients ranged between 2 and 82 years (mean: 46.3 years). It was the first episode of bullous FDE in six patients and a recurrence in the other four patients. The lag period between the drug administration and the eruption ranged from 2 to 96 hours (mean: 49 hours). Involvement of both skin and genital mucosa was present in seven patients, and affecting only the genitals in three patients. The most frequently involved genital site was the glans penis[6] (Figure 1), followed by the perineal area (four men and two women) and the vulva which was involved in both of the women (Figure 2). Genital FDE presented the same clinical aspect in all patients, consisting of superficial flaccid blisters and painful or itchy superficial erosions with an erythematous nonpigmented base.

A pharmacovigilance investigation was performed on all patients, and the Begaud algorithm was used to calculate the score of the likelihood causality. Table 1 shows the causative drugs associated with the genesis of bullous FDE with genital involvement. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the most common drugs involved in our patients. The Begaud algorithm score ranged from I3 in eight patients to I4 in two patients.

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Figure 1. Erythematous erosive patches on the glans penis induced by nonsteroidal anti-inflammatory drugs within 24 hours of administration.



Figure 2. Erosions on the vulva and the inner side of the thigh induced by paracetamol.

Drug cutaneous patch tests were performed in one patient on the residual plaque of FDE and were found positive to the suspected drug. A skin biopsy was performed in all patients, revealing necrotic keratinocytes in the epidermis leading to an epidermal detachment and a superficial and deep interstitial and perivascular infiltrate within the dermis composed of lymphocytes, eosinophil, and sometimes neutrophils, consistent with bullous FDE (Figure 3). Direct immunofluorescence was performed in three patients and was found negative.

Five patients were treated with topical corticosteroids, and the five other patients were treated with both oral and topical corticosteroids. A favorable outcome was observed in all 10 patients under treatment. The genital lesions faded without leaving residual hyperpigmentation, leading to a restitution ad-integrum.

Table 1. Drugs Associated with Bullous Fixed Drug Eruption with Genital Involvement

Drug involved	Number of cases	Begaud score
Nonsteroidal anti-inflammatory drugs	5	-
Ibuprofen (Ibuphil®)	1	I3
Mefenamic acid (Inflamyl®)	1	I4
Ketoprofen (Ketofen®)	1	I3
Tenoic acid (Toufilex®)	1	I3
Piroxicam (Roxam®)	1	I3
Antibiotics	3	-
Trimethoprim-sulfamethoxazole (Bactrim®)	2	I3
Doxycycline (Doxy®)	1	I4
Paracetamol	2	I3

DISCUSSION

Despite the small sample and the retrospective nature, our study highlights the atypical clinical and epidemiologic features of genital involvement in a severe form of FDE. The latter is considered a form of delayed-type hypersensitivity, mediated by CD8+ T cells, which occurs when patients become sensitized by a particular drug or its metabolites.[7] This phenomenon was first described in 1894 and since then an increasing number of drugs causing FDE have been reported.[2] Due to its uncommon clinical manifestations, the diagnosis of bullous FDE involving the genitals may be sometimes challenging, notably when affecting exclusively the genital mucosa, as was the case in three of our patients. In fact, the clinical presentation involving painful, burning, and itchy nonpigmenting erosive plaques can lead to mistakes. In addition, patients often do not relate their complaints to the use of drugs and the use of some drugs such as NSAIDs is occasional and usually forgotten by them.[5] A drug history should be pursued systematically and assiduously to avoid the delay in diagnosis, which can lead to severe or generalized recurrences if the offending drug is not discontinued. In cases of exclusive genital involvement, the differential diagnosis should include sexually transmitted diseases (e.g., herpes simplex virus and syphilis), erythema multiforme, pemphigus, mucous membrane pemphigoid, chemical burns, and pathomimia.[6]

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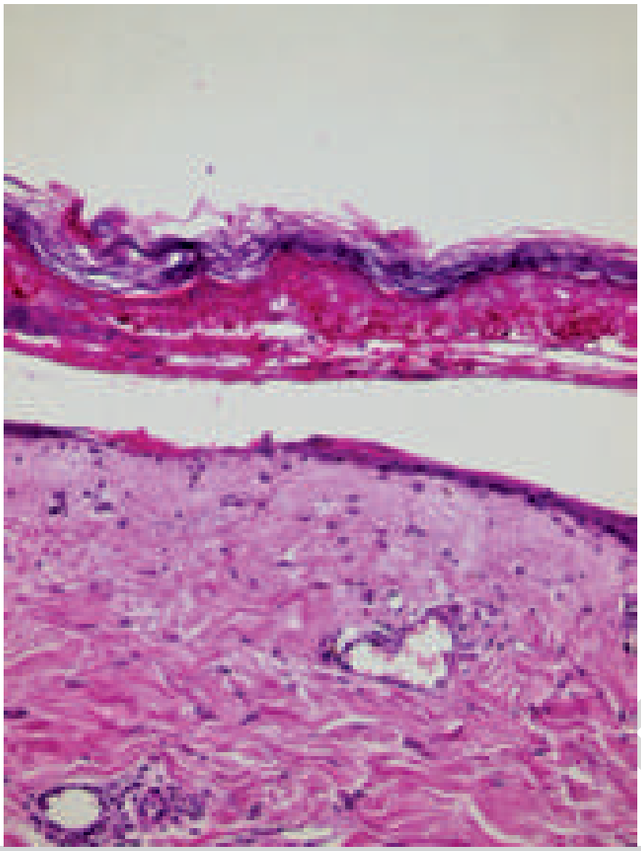


Figure 3. Presence of a subepidermal bullae containing fibrinous material with few eosinophils. Necrotic keratinocytes were present in the epidermis associated with hydrophobic degeneration of the basal membrane. Superficial dermal and perivascular inflammatory infiltrate made up of lymphocytes and eosinophils (HEx40).

In our patients and in all previous studies, genital mucosa was predominately affected in men.[8] We have no clear explanation for this finding. One possibility is that involvement of genitalia in women is harder to recognize.[9] It was also proposed that genital FDE could be a sexually inducible reaction. In fact, recurrent genital FDE cases were reported on men after every sexual intercourse with a female partner who was on a specific therapy for her own medical issue.[10] Although a lag period ranging from 30 minutes to 8 hours is usual between the drug administration and the eruption,[8] in some of our patients, it was as long as 2 days.

Histopathologic examination of the lesions revealed a basal cell degeneration leading to the formation of an epidermal detachment with a mononuclear cell infiltrate near the dermoepidermal junction, and sometimes the presence of macrophages in the dermis.[8] Historically, the most common drugs associated with FDE were sulfonamides, tetracyclines, and NSAIDs.[11] The list of drugs that reportedly cause genital involvement is steadily growing. Tetracyclines are a well-recognized cause of FDE.[12,13] Trimethoprim-sulfamethoxazole was the main cause of FDE on male genitalia in some recent studies.[14] In our study, NSAIDs were the most frequently drugs associated with genital bullous FDE.

In practice, drug identification is not always possible, especially when we are confronted with poly-medicated patients. In such cases, there are intrinsic and extrinsic scores that can help determine drug accountability. Intrinsic accountability is based on the anamnesis as well as the calculation of the Begaud score. Extrinsic accountability is based on the bibliographic data concerning the event and the drug in question and it varies from B0 (quite new effect) to B3 (well-known well-described effect).[15] The definitive diagnosis of drug accountability lies in patch testing with the suspected drug at the sites of involvement. It is a relatively safe and reliable method, which needs to be performed at least 6 weeks after resolution of the last acute episode of FDE. It is necessary to perform drug patch tests on the site previously affected by the FDE, especially if several drugs are involved. According to the recommendations of the European Society of Contact Dermatitis, patch tests can be made with the drug in its commercialized form diluted with 30% petrolatum.[16]

CONCLUSIONS

The diagnosis of bullous FDE is based mainly on clinical history and dermatologic examination, along with histologic findings and results of patch testing. Discontinuation of the culprit drug, as well as reassuring the patients about their condition, is the main aspect for the management of bullous genital FDE. Genital FDE causes apprehension, especially in men, about a possible venereal origin and their negative outcomes, such as sexual impotence and esthetic prognosis.[5]

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HISTORICAL DIAGNOSIS AND TREATMENT: ZOSTER

Diagnosis and treatments have advanced over the past century. This feature depicts conditions from a collection of stereoptic cards published in 1910 by The Stereoscopic Skin Clinic by Dr. S. I. Rainforth.



Courtesy of Dr. S. I. Rainforth

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Edward L. Keyes Resident Contest for Outstanding Case Reports

15th World Congress of the International Academy of Cosmetic Dermatology
Dresden, Germany June 18-20, 2020

Abstract deadline: March 1, 2020

To be awarded for the best Case Report submitted by a physician in training (resident, fellow, or registrar) for presentation at the 15th World Congress of the International Academy of Cosmetic Dermatology in Dresden, Germany June 18-20, 2020.

We invite you to submit original Case Reports that reflect the presentation of new ideas and original observations to the Academy membership and other attendees of the Congress. The case may be medical, surgical, and cosmetic (or combined) in nature.

The author whose abstract receives the highest score during the review process will receive a scholarship by the IACD to present the full paper at the 15th World Congress of the International Academy of Cosmetic Dermatology in Dresden, Germany June 18-20, 2020. The scholarship will provide reasonable travel expenses, lodging for 3 nights, the Congress registration fee, and a basic spending stipend.

Please submit your case report abstract via email to Vesna.M.Petronic-Rosic@medstar.net before noon, CDT, March 1, 2020. The abstract should be no longer than 2,500 characters including spacing. Material that was previously presented, published, or submitted for publication should not be offered. Applications will be graded based upon the educational value of the abstract and the extent to which it presents new and significant work. The Review Committee strongly recommends that abstracts have an organized, coherent, well-thought-out, and complete presentation. Please note that no paper submitted for consideration will be eligible if it has already been, or is in consideration for publication elsewhere at any time prior to the meeting. The winner(s) agree to publish their outstanding case report(s) in *SKINmed: Dermatology for the Clinician,* an official publication of the International Academy of Cosmetic Dermatology. By submitting your paper for consideration, you give *SKINmed: Dermatology for the Clinician* first-rights of refusal for publication through December 31, 2020. The applicant must be in training at the time of the Congress presentation.

All applicants will receive e-mail notice of the Resident Case Report Review Committee's decision by March 31, 2020.



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CORE CURRICULUM

Virendra N. Seghal, MD, Section Editor

Dermatitis Artefacta: An Update

Naveen Kumar Kansal, MD

Dermatitis artefacta is a specific psychocutaneous illness, in which the patient creates skin lesions to satisfy the unconscious need to presume a sick role. It is more common in women and in patients with a diagnosis of psychiatric illness/personality disorder (usually borderline) or external stressor. The clinical signs are characteristic and usually present with typical psychiatric manifestations. This diagnosis is by exclusion, and possible organic causes of cutaneous lesions must be ruled out. Treatment of dermatitis artefacta is taxing, both on the physician as well as on relatives, and it needs to involve a multidisciplinary approach consisting of dermatologists and mental health professionals. (*SKINmed*. 2019;17:311–316)

Factitious disorders are defined as self-harming "behaviors" in many forms, leading to subjective and clinically relevant harm but are not directly linked to suicidal intent.[1] It is significant to note that physicians are expected to believe in their patients' history and clinical signs. Some patients may have inappropriate belief systems, for example, information from the internet or media, or belief in faith-healers/seers, and this behavior does not necessarily constitute a factitious disorder behavior.[2] Patients with factitious disorders will intentionally produce physical harm or psychologic symptoms so as to lead to deceiving clinical signs in themselves (or others). These disorders affect about 0.05%–0.40% of the general population, and although the disorder may be seen in any clinical setting, the prevalence is estimated to be the highest in dermatology (approximately 2% of all patients in clinical dermatology units);[1,3] therefore, the socio-economic burden of these disorders cannot be over-emphasized.[4] A proposed classification of factitial dermatoses is presented in Table 1.[1,2] The focus of this article is to provide a brief overview of the dermatitis artefacta (DA) syndrome.

DEFINITIONS

By definition, the word artifact refers to "an object produced or shaped by human workmanship"[5] or "an object that is made by a person, such as a tool or a decoration, especially one that is of historical interest."[6] These artefacts may be produced for a number of reasons, for example, tattooing seen in football or cricket players, scarifications, or nose and ear piercing. Tattooing of the names of patients with Alzheimer's disease or other mental disorders has also been used.[7]

In contradistinction, DA is a dermatologic manifestation of the factitious disorder (Table 2),[8] in which patients consciously and deliberately produce mucocutaneous lesions to fulfill an unconscious desire to assume a primarily sick role and be cared by someone; therefore, the patients seek the "primary gain" of the emotional and psychologic benefits that accrue to those who are "ill." Patients escape the responsibility of their actions from the treating physicians and give inconsistent history, incompatible with the clinical findings. DA thus can be considered a physical "sign" (to diagnose), in contrast to a disease.[9]

EPIDEMIOLOGY

The actual prevalence and incidence rates of DA are not known; however, it is generally accepted that it may be more common than usually suspected/diagnosed. The sex ratio is also variable; in prepubertal children, the ratio is equal.[10] In adolescents and adults, however, women outnumber men (F:M = 3:1 to 20:1).[11–13] These studies imply that most of the cases begin in adolescence and in adults[5]; the highest incidence is in late teens or the early twenties.[1,5,14] Onset in the older age group is rarer, but in this group, sex ratio is reversed (F:M = 1:2).[15] Early studies suggest

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Table 1. Classification of Self-Inflicted Dermatoses[1,2]

Dermatitis artefacta (dermatitis artefacta syndrome; unconscious self-harm)
Dermatitis paraartefacta (dermatitis paraartefacta syndrome)
Münchhausen syndrome (factitious disorder imposed on self) Münchhausen syndrome by proxy (fabricated and induced illness; factitious disorder imposed on another)
Malingering (usually short-term opportunistic behavior [deception] for external incentive)
Gardner–Diamond syndrome (psychogenic purpura)

Table 2. Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), Criteria for Factitious Disorders[8]

Factitious disorder imposed on self A. Falsification of physical or psychologic signs or symptoms, or induction of injury or disease, associated with identified deception. B. The individual presents himself or herself to others as ill, impaired, or injured. C. The deceptive behavior is evident even in the absence of obvious external rewards. D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.
Factitious disorder imposed on another A. Falsification of physical or psychologic signs or symptoms, or induction of injury or disease, in another, associated with identified deception. B. The individual presents another individual (victim) to others as ill, impaired, or injured. C. The deceptive behavior is evident even in the absence of obvious external rewards. D. The behavior is not better explained by another mental disorder, such as delusional disorder or another psychotic disorder.

factitious dermatosis being more common in health-care workers and/or their families.[16] Medical information has been usually extensive in this patient group;[5] however, in today's era of free and up-to-date medical knowledge available through the internet and other media resources, this difference is probably becoming less obvious.[2,9,13] In factitious conditions, interestingly, females are more likely to have *actual* physical damage than males.[17]

ETIOLOGY

DA has been considered a psychiatric problem in dermatology as "a cry for help."[18] A preceding psychosocial stressor can be present in many cases. The lesions may develop in the setting of a dissociative phenomenon.[19–21] There may be conflict or fear of authorities, for example, school phobia/bullying in children or a history of past traumatic experiences (physical or sexual abuse). Inappropriate/immature coping styles may be present. The relationships between family members may be strained and can act as precipitant. There may be associated depression with an inescapable sense of anhedonia, despair, and generalized boredom in many cases.[5,22] Patients may have personality disorders, most commonly the borderline personality disorder,[23,24] but also the hysterical and paranoid ones.[2,5] The psychopathology underlying the patient's motivation for the sick role is a complex interplay of many factors. Being sick is an actual "process" of the illness.[25] People will differ in the ways in which they perceive, act, or do not act on the symptoms of the disease they experience. This has been considered the patient's personal "illness behavior." This illness behavior would shape the role within the family and also with the health-care personnel.[2,25] The patients expectedly are exempted from their responsibilities and show regression. DA in the chronic form may also be associated with eating disorders as a disorder of body image. This has been suggested by the association with borderline personality disorder as well as clinical experience.[26]

CLINICAL FEATURES

DA can be considered a physical "sign" to be recognized by examining physician.[9] One of the most important features in the clinical picture are these signs and their sudden and striking development, for example, appearance during sleep and to be "noted" by the patient on waking up.[27] A second classic clinical feature is an empty or "hollow" history:[5,28] almost a sudden appearance of all lesions without a clear explanation of how they appeared. The history of progression of each lesion from its initial stage is conspicuous by its absence; however, the patient may be ready with an elaborate and detailed description of complications and the failure of the lesions to improve or heal.

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Usually, patients use no more than one single method to produce these lesions which, therefore, are likely to be monomorphic but may be in different stages of developments.[16,29] Considerable scarring may be present as well.

At the initial encounter, the patient, commonly a young woman, presents with these dramatic skin lesions in an unusually calm manner and sometimes with a friendly gesture (or with a "*Mona Lisa smile*") to the physician;[2] however, considerable anger, anxiety, and suspiciousness are apparent in the family members including disappointment with prior multiple unsuccessful attempts at treatment.[9] The condition may remain misdiagnosed for long, even up to a decade or more after the appearance of initial clinical signs.[18,30] On cutaneous examination, lesions characteristically do not have any discernible pattern of known dermatoses. The margins are usually sharp with a clear demarcation from normal skin. The borders of the lesion are angulated and geometric, and the surface may have crusting, atrophy, or necrosis. If caustic liquids were used to produce lesions, then typical linear tracks on the skin will be seen. The most common site for lesions is the face in all age groups.[10,31] Lesions may also be present on the chest, back and extremities abdomen, scalp, or genitalia. Whether single or multiple, all lesions are usually within reach of the hands, usually the dominant one.[13] In women, lesions may be present on the breasts with significant mutilation.[32–34]

PSYCHIATRIC COMORBIDITIES AND COMPLICATIONS

About one-fifth of DA patients have somatization disorder and hypochondriasis.[35] They also often commonly have anxiety, substance abuse, and depression.[10,31] Borderline personality disorder is recognized as an important factor for chronicity of disease in both sexes. Other reported associated psychiatric illnesses include schizophrenia,[36] trichotillomania,[37,38] and attention-deficit hyperactivity disorder.[39]

The various deceiving presentations and complications of DA include the following:[40]

1. Recurrent periorbital cellulitis[41]
2. Skull erosion and intracranial infection[42]
3. Cerebral abscess[43]
4. Deep fungal infections (e.g., due to *Exophiala*[44])
5. Keloids and foreign body granuloma[45]
6. Malignancy[46]
7. Marjolin's ulcer[47]
8. Contact dermatitis and panniculitis[48,49]
9. Genital scars[50]
10. Genital artefactual ulcers as "*folie à deux*"[51]
11. Bullous lesions due to deodorant spray[52–55]
12. Lesion induction by one of the patient's multiple personalities[20]
13. Osteomyelitis[2]
14. Pseudo-cheilitis[56]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Effective management of these patients is possible only after considering both dermatologic and psychiatric differential diagnoses.[5] The dermatologic diagnosis depends on the age and sex of the patient and on presence of a characteristic history, the indifference of the patient in spite of lesions that are cosmetically unsightly and which are likely to be painful, along with the considerable anger and restlessness of attending family members/relatives, and the peculiar morphology of the mucocutaneous lesions. The lesions should be differentiated from serious morbidities, for example, malignancies,[38,46,57,58] cellulitis,[38,41] sexual abuse,[59] pyoderma gangrenosum,[60–63] photodermatoses,[64] immunobullous diseases,[65,66] reflex sympathetic dystrophy,[67] vasculitis,[68,69] and the collagen vascular diseases.[5] The pathologic evaluation of lesional biopsies usually reveals non-specific epidermal and dermal changes and inflammation; however, it has been suggested that a diagnosis of DA should be considered if pathologic findings include intra-/subepidermal blistering with mild inflammatory infiltrate, rupture of collagen fibers, multinucleated (more than five nuclei) keratinocytes (a morula-like appearance), or elongated and vertically aligned keratinocyte nuclei.[3,70–72] The serial use of standardized photography along with Wood's light examination has also been described as a diagnostic aid.[73] Among the psychiatric conditions, body-focused repetitive behavior disorders, delusional infestation or delusion of some other foreign invader, Morgellons' syndrome, Munchausen's syndrome, and malingering all need to be considered and excluded.[47,74–77] DA is a diagnosis of exclusion.[40] Typically, patients are usually otherwise healthy and have normal laboratory parameters.[78]

PROGNOSIS

The prognosis is usually poor.[79] Approximately 30%[80] to more than 50% of patients will have chronic disease and usually have a personality disorder (commonly borderline) with a need for psychologic assessment.[31] In a long-term follow-up study of 43 patients, 13 patients continued to produce lesions or were disabled with other psychiatric disorders for more than 12 years after the onset of the disease. Prognosis depends upon the circumstances of the patients' life rather than treatment.[80] DA has also been shown to have a considerable impact on the quality of life scores.[81]

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MANAGEMENT

The management of DA is very challenging. The crucial step in effectively treating a DA patient is establishing a strong therapeutic rapport. Trust and honesty in the physician–patient relationship will increase compliance. A nonconfrontational approach is preferable to an assertive or audacious interaction,[2,27] which may lead to the breakdown of the physician–patient relationship early in therapy. It is important to be non-judgmental as well.[40] A combined approach with both dermatology and psychology professionals is suggested as suitable and has improved outcomes.[18,31,40] Therapy should be planned to reach three main aims.[2] First, the cutaneous damage must be minimized and treated; for infections, topical and systemic antibiotics should be administered. Topical therapy may be used under occlusion[18,82]; some workers have utilized aluminum foil in the dressing, with the disruption to the foil providing an important pointer to dressing manipulation by the patient.[47] Second, adequate time should be devoted to recognize the psychiatric problem. The patient needs to be allowed to express his or her problems in confidentiality. The approval of the "cry for help" has the advantage of a non-aggressive interaction and particularly useful in the pediatric age-group. Third, adult patients usually respond to another method of nonconfrontational approach. This has been equated with "a narrow escape," or "face-saving recovery" or "a quasi-confession," or "an escape with honor" plan. This basically works as the patient, who also wants a solution to his or her problems may propose a plan.[2,5]

Pharmacotherapy with psychotropic agents, for example, selective serotonin reuptake inhibitors (SSRIs; fluoxetine, sertraline, paroxetine, escitalopram,[83] etc., usually in higher dosage range) and low-dose atypical antipsychotics (e.g., risperidone, olanzapine, aripiprazole, ziprasidone), is known to help DA patients;[84] however, the mainstay of therapy is to address the underlying issues causing the presenting clinical features. Cognitive behavioral therapy aims to target the underlying pathologic behavioral patterns and/or issues with self-esteem and confidence.[27,85] Relaxation techniques and psychotherapy are also useful; however as noted before, the prognosis depends on the patient's life circumstances rather than the treatment.[80] Long-term prognosis is likely to be improved if an underlying psychiatric issue has been duly addressed and accepted by the patient. With subsequent customized management, the patient is likely to see clinical improvement.[40,85]

CONCLUSIONS

DA is a relatively uncommon dermatologic condition that should be considered in the presence of bizarre clinical features and when investigations do not yield an alternative diagnosis. Patients are usually unaware of the cutaneous damage and usually have a history of underlying stress or psychologic disorder. Although skin biopsies are usually nonspecific, some recent studies have indicated a few specific pathologic features like what. Except in milder cases induced by immediate stress, the prognosis for a cure is poor. The illness usually fluctuates with the circumstances of the patient's life. A multidisciplinary team consisting of dermatologists and mental health professionals has been shown to improve the prognosis.

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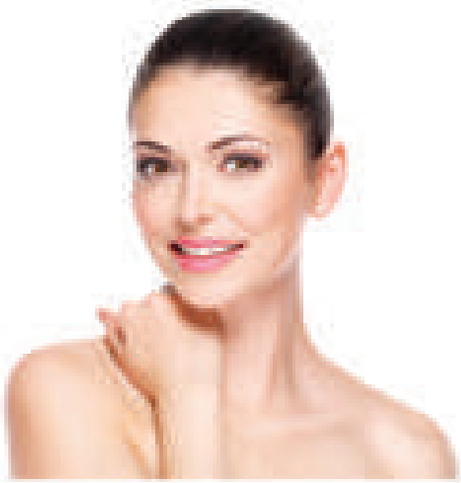


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THE HEYMANN FILE

Warren R. Heymann, MD, Section Editor

Striae Due to Bartonella Is a Stretch

Warren R. Heymann, MD

I met a woman in her early 20s who is being treated for chronic Lyme disease and *Bartonella* infections with multiple courses of antibiotics. During my examination, I noted several old white atrophic striae on her hip and leg. Her mother, who was accompanying her, stated matter-of-factly, "Those are due to her *Bartonella* infection. They started out red." My response was that striae routinely do that—they are initially red to violaceous, before turning white.

I listen to my patients—over the years, I have continually learned from them. Even though I was admittedly skeptical, I thought I should examine the current medical literature to determine if *Bartonella* can cause striae.

LYME COINFECTIONS

Patients with complex medical symptoms, including fatigue, headache, and poor appetite, in whom a definitive diagnosis cannot be rendered are thought by some to have chronic Lyme disease with coinfections with *Anaplasma*, *Babesia*, or *Bartonella*.

As a dermatologist, I shall limit my Commentary to striae; however, it must be acknowledged that the concept of these chronic infections is controversial, at best. Five systematic literature searches using Boolean operators and the PubMed search engine were performed. The authors acknowledged the expectation that ticks contain *Bartonella* DNA—ticks feed on a variety of mammalian hosts that may be reservoirs for *Bartonella* spp. The presence of *Bartonella* DNA in the tick does not prove that the tick is a competent vector for transmission to a second mammalian host. The authors concluded: "The *Ixodes* spp. ticks that transmit *B.* [*Borrelia*] *burgdorferi* are capable vectors of several human pathogens. In all cases, however, these infections produce defined clinical syndromes that are corroborated by objective clinical and laboratory findings. This is true for well-established Babesia-Lyme and Anaplasma-Lyme coinfections ... There is little evidence to support tick-borne *Bartonella* infection or *Bartonella*-Lyme coinfection."[1]

UNDERSTANDING STRIAE

The precise pathogenesis of striae is unknown; however, in otherwise healthy individuals, they are thought to occur when excessive stretch overwhelms the dermal integrity of the skin, resulting in a wound-type response with abnormal and/or incomplete repair. Striae also observed in pregnancy (striae gravidarum), Cushing syndrome, and Marfan syndrome, and with use of topical steroids. Significant remodeling of dermal elastin fibers with truncation and realignment has been observed.[2]

Twenty-eight pregnant women with striae gravidarum had skin sample biopsies of recently developed, erythematous abdominal lesions that were examined by multiphoton microscopy and immunostaining for protein expression and localization of type I procollagen. Real-time polymerase chain reaction was used to determine gene expression levels. The authors were able to demonstrate that early striae gravidarum displays marked separation and disorganized collagen fibrils that fail to form bundles. These alterations may reflect ineffective repair of collagen bundles disrupted by intense skin stretching. Persistent disruption of the collagenous extracellular matrix likely promotes the formation and atrophy of striae gravidarum.[3] Additionally, the estrogen receptor has been demonstrated to be upregulated in affected skin, suggesting a role for hormonal influences in the development of the lesion. [2]

My PubMed search of the literature for histologic evidence of striae and *Bartonella* yielded one case: an 18-year-old man with illness of 3 years' duration, whose symptoms included fatigue, headaches, and fine tremors. His physical examination demonstrated red conjunctivae, cervical lymphadenopathy, and erythematous striae involving both legs and the buttock. Histopathology of a skin lesion over the right deltoid contained features of a blue nevus. A lesional biopsy of striae from the left thigh contained minimal nonspecific superficial perivascular chronic inflammation. Immunostaining of the striae tissue from his skin biopsy revealed immunopositive staining

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for *Bartonella henselae* within the dermis; confocal microscopy imaging showed the bacteria to be external to the vascular tissue. DNA was amplified and successfully sequenced from the striae biopsy sample. *Bartonella* spp. DNA was not amplified from the biopsy of the blue nevus.[4]

Even if confirmed by other studies, an association does not equate with causation—this was not a fulfillment of Koch's postulates. The fact that the organism is not present in the above patient's blue nevus does not imply pathogenesis where it is found. His striae were in an inflammatory stage; the blue nevus (presumably) was not. Perhaps the inflammation alone could have predisposed a tissue affinity for the organism, which could be an innocent bystander.

A study was performed of 12 boys (11 to 17 years old) with horizontal striae distensae (SD) of the lower part of the back, conducted by telephone surveys and medical chart reviews. The impetus for the study was based on "common concerns that these boys were using unmonitored exogenous steroids, had a metabolic condition, or were infected with *Bartonella henselae* (cat-scratch disease) or *Borrelia burgdorferi* (Lyme disease)." In their retrospective review, titers of *B. henselae* and borreliosis were only determined in one of the patients before he was referred to pediatric dermatology, which limited their ability to exclude the possibility of infection as the trigger for SD. (There was no serologic evidence of infection.) None of the boys had a history of unmonitored injectable or oral anabolic steroid use. The authors concluded that horizontal SD of the lower back in adolescent boys is associated with rapid growth spurts, tall stature, and a positive family history of SD. This suggested that SD are a normal physiologic process in growing adolescent boys rather than a sign of underlying pathology.[5]

CONCLUSIONS

There are not enough data to completely rule out the theory that rare cases of striae may be caused by *Bartonella* infection. I surmise that the answer could be determined by inoculation of *Bartonella* in an appropriate animal model. Based on the current literature, any pathogenic association of *Bartonella* with striae is a real stretch.

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Sylvia Hsu, MD, Section Editor

Doxycycline Is Safe for Short-Term Use in Children of All Ages

Margaret E. Hemphill, BS;[1] Nicholas K. Mollanazar, MD;[2] Sylvia Hsu, MD[1]

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Doxycycline is safe for short-term therapy in children under 8 years of age by the American Academy of Pediatrics.


No evidence to support the claim that doxycycline is associated with dental staining in children.

In the 2018 *RedBook*, The American Academy of Pediatrics (AAP) updated the recommendation for the use of doxycycline in children younger than 8 years.[1] The new guidelines state that doxycycline is now considered safe for short-term use (21 days or fewer) without regard to the child's age. Doxycycline has been rendered the best treatment for survival of Rocky Mountain spotted fever (RMSF) and remains an effective treatment for other tick-borne diseases, such as Lyme disease.

Doxycycline is widely used in dermatology practice to treat acne, rosacea, and bacterial infections. When doxycycline was first introduced in 1967, the Food and Drug Administration (FDA) automatically assigned the antibiotic the same list of safety precautions as that of tetracycline. The prescription of tetracycline has been largely avoided for young children due to its ability to chelate calcium. This chelation may lead to tooth discoloration (yellow, gray, or brown) and dental enamel hypoplasia during odontogenesis, which is typically complete by age 8. Doxycycline, however, does not chelate calcium as readily as tetracycline. As a result, the AAP has now provided recommendations exclusive for doxycycline. To date, there is no conclusive evidence suggesting that short-term doxycycline use results in dental complications in children.

A recent study[2] reported results from a retrospective cohort study that found no evidence of doxycycline-induced dental staining in 58 children before the age of 8. An average of 1.8 antibiotic courses and a dose of 2.3 mg/kg of doxycycline were administered to each child. A blind, randomized, controlled study[3] found that doxycycline treatment was not associated with tooth discoloration in children aged 2–8 years with an average of 2.0 antibiotic courses. A third study[4] found that doxycycline restrictions should be lifted for children under 8 years of age if the daily dose does not exceed 200 mg/day. This recommendation was based on a report[5] that found limited evidence for reversible tooth discoloration in four patients following 30- to 45-day courses of doxycycline therapy at a dosage of 200 mg/day. The evidence presented by each of these studies supports the AAP's recommendation that doxycycline use in children under 8 years of age is safe given that the treatment is short term, and the dosage does not exceed 200 mg/day.

CONCLUSIONS

Overall, this change by the AAP should have positive effects on the quality of healthcare for children. Doxycycline is a highly effective and inexpensive treatment option with a broad-spectrum classification, although often more expensive or less effective treatments are prescribed. Short-term doxycycline therapy during odontogenesis is not associated with tooth discoloration. The treatment of tick-borne diseases and skin conditions, among others, will become safer, highly efficient, and cost-effective as recommended by the 2018 *RedBook*.

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CASE STUDY

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

Gorlin-Goltz Syndrome: A Rare Syndrome Presenting as an Even Rarer *de Novo* Case with Numerous Features and Complications

Caroline Galdes, MD, MSc, MRCPGP(Int);[1] Dillon Mintoff, MD, MSc, MRCP(UK);[2]
Eileen Clark, MD, MRCP(UK)(Derm)[2]

A 76-year-old woman with intellectual deficit presented with a small, pearly, telangiectatic raised lesion on the left cheek, together with an ulcerated lesion on the right side of the nose (Figure 1), which were clinically diagnosed as basal cell carcinomas (BCCs.) These were treated with cryotherapy. The patient had had a right hemimandibulectomy (Figure 1), and she showed frontal and temporal bossing and a wide nasal bridge. (*SKINmed*. 2019;17:324–327)

Gorlin-Goltz syndrome, also known as Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is caused by a mutation in the tumour suppressor gene Protein patched homolog (PTCH) gene found on chromosome 9. This gene is essential in embryonal development, control of cell division and growth of tumour. Several mutations may result in this syndrome. Prevalence is estimated to be about 1 in 60,000 with an equal male to female ratio.

Over the course of a few months, three other BCCs (two on the upper lip and one on the right temple) developed, which were treated with cryotherapy. She also developed a lesion on the left lateral canthus, which was excised and histologically proven to be another BCC. The patient had a history of previous multiple BCCs in sun-exposed areas, including an ulcerated BCC on the left shin that had proven to be invasive to the junction of the papillary and reticular dermis.

At 42 years of age, the patient had been seen by ear, nose, and throat specialists due to bony swelling of the ramus of the right mandible, which had been complicated by abscess and sinus formation. A biopsy of the lesion showed numerous cysts, lined by a flat thin regular layer of keratinizing squamous epithelium, which were diagnosed as keratocysts. Initially, the abscess was excised and drained extraorally, and this was followed by right partial hemimandibulectomy. Further cysts later developed in the remaining part of the mandible, which were initially treated by enucleation but required removal of the remaining hemimandible 13 years later. During the same procedure, a BCC on her right cheek was excised.

At 57 years of age, the patient presented with postmenopausal bleeding. Curettings showed moderately differentiated endometrial papillary adenocarcinoma, requiring a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Histology showed a hemorrhagic tumor within the uterine cavity, without invasion. Additionally, the left ovary had a stony hard consistency with a benign calcified fibroid in it.

Computed tomography of the brain showed bilamellar calcification of the falx cerebri and tentorium cerebelli (Figure 2). She also had scoliosis and pectus carinatum. In recent years, the patient had also developed multiple chalazions, which had been removed. Due to the large number of BCCs developing within a few months, she was started on acitretin, which decreased the rate of occurence of BCCs.

DISCUSSION

Gorlin-Goltz syndrome, although first described in 1894, was established as a syndrome in 1960.[1] It is caused by an abnormality in the *PTCH1* tumor suppressor gene, found on chromosome

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Figure 1. Right hemimandibulectomy and basal cell carcinoma on the right side of the nose.



Figure 2. Computed tomography scan showing bilamellar calcification of the falx cerebri, one of the major criteria of Gorlin-Goltz syndrome.

9.[1] In the absence of its ligand, *PTCH1* acts as a cell cycle regulator controlling differentiation and growth.[2,3] Two mutagenic hits are required for tumor suppressor gene inactivation. When this occurs, tumors, such as BCCs, odontogenic keratocysts, and medulloblastomas, grow with loss of heretozygosity.[2]

Gorlin-Goltz syndrome is multisystemic, involving skeletal abnormalities, ectopic intracranial calcifications, as well as ocular, genitourinary, and cardiovascular system findings, but the basic features are BCCs, mandibular cysts, and skeletal defects.[1]

Occurrence of BCCs varies between ethnic groups, being less frequent in dark-skinned races.[1,4] BCCs in this syndrome tend to be more aggressive.[4] Management options are vast, including topical chemotherapy, cryosurgery, surgical excisions, laser ablation, and photodynamic therapy.[5] Currently, radiation is not recommended, as it can cause invasion of BCCs and also makes the irradiated skin more prone to developing additional BCCs.[5,6] Additionally, ultraviolet light exposure is positively correlated

Table I. Diagnostic Criteria for Gorlin-Goltz Syndrome[4]

Major criteria
1. More than two basal cell carcinomas, or one in patients less than 20 years old
2. Odontogenic keratocysts of the jaws proven by histopathology
3. Palmar or plantar pits (three or more)
4. Bilamellar calcification of the falx cerebri
5. Bifid, fused, or markedly splayed ribs
6. First-degree relatives with NBCCS
Minor criteria
1. Macrocephaly determined after adjustment for height
2. Congenital malformation: cleft lip or palate, frontal bossing, "coarse face," moderate or severe hypertelorism
3. Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
4. Radiologic abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame-shaped lucencies of the hand and feet
5. Ovarian fibroma
6. Medulloblastoma

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with an increased risk of BCCs;[4] meanwhile, vitamin A analogs may prevent new skin malignancies.[7]

Odontogenic keratocysts occur commonly in the first few decades of life and are the most consistent feature of NBCCS.[1,2] Mandibular cysts are more common than maxillary cysts, and the posterior regions are most commonly affected.[2,5,8] This was seen in the case illustrated.

Odontogenic keratocysts can be treated conservatively by enucleation (complete separation of the lesion from adjacent bone) with or without curettage (removing the lesion with part of the adjacent bone), or aggressively by ostectomies (using rotary cutting instruments to remove the lesion with part of the adjacent bone), resection, or chemical curettage. Aggressive methods of clearance contribute to prevention of recurrent keratocysts. En bloc resection is necessary in recurrences, despite multiple treatments, due to multilocular aggressive keratocysts and multiple keratocysts.[2]



Figure 3. Chest radiograph showing marked right-sided scoliosis, an associated skeletal abnormality in Gorlin-Goltz syndrome.



Figure 4. Pectus carinatum and scoliosis, associated features of Gorlin-Goltz syndrome.

Diagnostic criteria for NBCCS (Table I) were established in 1993 and modified in 1997.[8] This syndrome is diagnosed when two major or one major and two minor criteria are present.[1] The case reported here is of a patient with three major and four minor criteria: multiple BCCs, multiple keratocysts in the mandible, bilamellar calcification of the falx cerebri and tentorium cerebelli (Figure 2), macrocephaly, ocular hypertelorism, frontal bossing, and coarse face, pectus carinatum (Figure 3), scoliosis (Figures 3 and 4), and ovarian fibroma. In this case, the patient had no first-degree relatives with Gorlin-Goltz syndrome.

Several features are associated with this syndrome.[4] Associated features present in this case are provided in Table II. So far, no laboratory test is available for the diagnosis of Gorlin-Goltz syndrome; however, high levels of cyclic adenosine monophosphate may be present in affected patients.[9] Additionally, a diagnostic protocol (Table III) has been developed to assist in the examination of individuals suffering from this syndrome.[1,10]

Table II. List of Associated Features Reported in This Patient

System	Feature
Ocular system	Chalazions
Musculoskeletal system	Scoliosis Pectus carinatum
Genitourinary system	Endometrial carcinoma
Central nervous system	Intellectual deficit

Table III. Diagnostic Protocol

1. Family history: past medical and dental history
2. Clinical examination: oral, skin, central nervous system, head circumference, interpupillary distance, eyes, genitourinary system, cardiovascular system, respiratory system, skeletal system
3. Genetic testing
4. Radiographs: chest, anteroposterior and lateral skull, panoramic radiograph, cervical and thoracic spine, hands and pelvis
5. Ovarian ultrasound for ovarian fibroma
6. Echocardiogram for cardiac fibroma

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Early diagnosis permits monitoring for the development of aggressive BCCs and medulloblastomas.[1,5–7,10] Frequent follow-up is necessary, as odontogenic keratocysts and BCCs are formed almost continuously.[9] Additionally, genetic counseling is required due to the autosomal dominant inheritance.[3,9,10] Antenatal diagnosis can be performed using ultrasound scanning and DNA analysis of fetal cells obtained by amniocentesis.[1,7]

A multidisciplinary approach is necessary in the diagnosis and treatment of this syndrome;[1] it should include dermatologists, dentists, neurologists, obstetricians and gynecologists, geneticists, and other health professionals such as speech and language pathologists who may encounter such patients during rehabilitation after hemimandibulectomy.

CONCLUSIONS

The case illustrated depicts the clinical history of a patient with Gorlin-Goltz syndrome, who exhibited multiple major and minor criteria for the diagnosis, and multiple associations with this syndrome. Life expectancy is not significantly altered; however, complications can cause considerable morbidity.[2,4,7]

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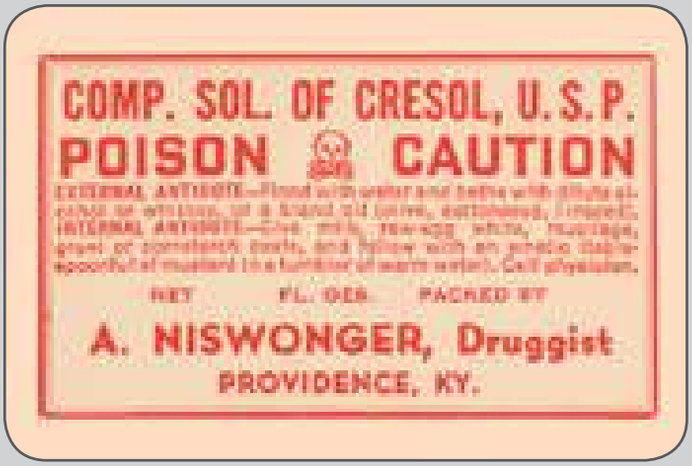
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CASE STUDY

Waistband Mycosis Fungoides: A New Clinical Variant of Early-Stage Disease

Chee Won Oh, MD;[1,2] Amy Thorne, DO;[3] Taylor Duke, MD;[4] Daniel J. Lewis, BA;[1,5] Rakhshandra Talpur, MD;[1] Madeleine Duvic, MD[1,*]

Case 1: A 17-year-old white man was referred for evaluation of biopsy-proven patch-stage mycosis fungoides (MF) that had first appeared 5 years previously. Asymptomatic "bruises" had appeared under his football padding in a waistband distribution, and these lesions improved during each offseason but never fully resolved. His exposure history was only positive for swimming pool water and his athletic pads. On physical examination, large, irregular, geometric tan-colored patches were present along his waistband area, in areas of contact with his football padding, with an involved body surface area (BSA) of 23.7% (Figure 1A). Examination of scale for fungal hyphae under potassium hydroxide was negative. No lymphadenopathy was present. (*SKINmed*. 2019;17:329–332)

A biopsy of a pink, scaly patch on the left lower abdomen showed changes consistent with MF. Immunohistochemical studies demonstrated CD3+ lymphocytic infiltrates with an increased number of CD4+ cells and partial loss of CD7 in the epidermal and dermal lymphocytes. The dermal ratio of CD4+ to CD8+ cells was approximately 3:1 to 4:1. Monoclonal T-cell receptor β- and γ-chain gene rearrangements were detected by polymerase chain reaction. Laboratory studies and flow cytometry of the blood for aberrant T-cell populations were normal.

The patient was diagnosed with stage IB MF (T2aN0M0B0). He was treated with narrow-band ultraviolet B therapy three times per week and topical triamcinolone 0.1% cream for 2 months without improvement. Bexarotene 1.0% gel, applied to the lesions for 3 months, led to a partial response with a reduction of the affected BSA to 1.5%. Six months later, the waistband lesions had been cleared completely (Figure 1B).

Case 2: A 77-year-old Caucasian man was referred for evaluation of an erythematous eruption that had rapidly appeared around his waistband and then remained stable for 2 years. Biopsies taken from the skin of the right side of the chest and waist showed evidence of early patch-stage MF. On physical examination, no lymphadenopathy was present. Examination showed bright red, coalescing patches along the waistline area affecting 9% of his BSA (Figure 1C).

A Fite stain of a skin biopsy was negative for acid-fast bacilli, excluding leprosy. A clonal rearrangement of the T-cell receptor gene was detected by polymerase chain reaction in both samples. His staging workup included abnormal results of peripheral blood flow cytometry, which showed 24.6% CD3+/CD4+ cells (normal 32.3% to 63.8%), 58.4 % CD3+/CD8+ cells (normal 10.8% to 36.3%), and 1285 CD8+ cells/μL (normal 78 to 746 μL). He also exhibited high serum β_2-microglobulin, high thyroid-stimulating hormone, and low immunoglobulin G concentrations.

The patient was diagnosed with stage IA MF (T1aN0M0B0). Treatment with topical triamcinolone 0.1% cream for 7 months resulted in a complete response without recurrence at 14 months of follow-up (Figure 1D).

Case 3: A 41-year-old Caucasian man reported a 4-year history of a nonpruritic, erythematous eruption around his waistband

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Figure 1. (A, B) Waistband mycosis fungoides (MF) in a 17-year-old Caucasian man (case 1). (A) At the initial visit, geometric hyperpigmented lesions were present along the waistband area, where there was contact with football pads. (B) After 6 months of applying topical triamcinolone 0.1% cream and bexarotene 1% gel, the lesions had completely resolved. (C, D) Waistband MF in a 77-year-old Caucasian man (case 2). (C) At the initial visit, bright-red, coalescing patches were present along the waistline area. (D) Treatment with topical triamcinolone 0.1% cream for 7 months resulted in complete response with residual hyperpigmentation. (E, F) Waistband MF in a 41-year-old Caucasian man patient (case 3). (E) At the initial visit, confluent, pink scaly patches in a bathing trunk distribution were seen after the patient had applied Selsun Blue shampoo, causing irritation. (F) After 5 months of treatment, there was a partial response, with folliculitis present on the left lower region of the abdomen.

that had later extended to his groin and buttocks. A biopsy of the skin over the right hip showed an acanthotic epidermis with focal spongiosis. Atypical lymphocytes and histiocytes were present in the epidermis and superficial dermis. The epidermal lymphocytes were predominantly CD8+, whereas the dermal lymphocytes were predominantly CD4+. Clonality studies for T-cell receptor β-gene rearrangements were positive.

No lymphadenopathy was present. On skin examination, circumferential confluent pink scaly patches in the bathing trunk distribution and hypopigmented patches in the axillae involving12.2% of his body surface were observed (Figure 1E). Peripheral blood flow cytometry demonstrated no aberrant T-cell populations.

He was diagnosed with stage IB MF (T2aN0M0B0) with CD8+ predominance. Fifteen months after treatment with topical triamcinolone 0.1% cream and ultraviolet B therapy, he exhibited a partial response, with reduction of skin lesions to 6% of his BSA (Figure 1F). Topical nitrogen mustard 10 mg/100 mL ointment induced an allergic reaction and was subsequently discontinued. Fifteen months after the initial visit, his affected BSA had decreased to 4%.

DISCUSSION

MF, the most common cutaneous T-cell lymphoma, shares clinical manifestations with many other cutaneous diseases.[1] The diagnosis of early-stage MF can be particularly difficult because of heterogeneous clinical presentations and histologic findings that overlap with those of eczema or psoriatic dermatitis.[2] To date, more than 20 forms of MF have been described (Table).[2–5]

MF is thought to arise from chronic antigen-driven clonal expansion and loss of activation-induced cell death, leading to the accumulation of effector memory T cells in the skin.[6,7] *Staphylococcus aureus* is capable of inducing T-cell proliferation due to superantigens,[8] and eradication of *S. aureus* has been shown to be clinically

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Table. Variants of mycosis fungoides (MF)

Classic MF
Anetodermic MF
Bullous MF
Erythrodermic MF
Folliculotropic MF
Granulomatous MF
Hypopigmented MF
Ichthyosiform MF
Interstitial MF
Invisible MF
Lichenoid MF
MF with epidermal mucinosis with a spongiosis-like pattern
MF with eruptive epidermoid cysts
Pagetoid reticulosis
MF palmaris et plantaris
Papular MF
Pigmented purpuralike MF
Poikilodermatous MF
Pustular MF
Solitary MF
Syringotropic MF
Unilesional MF
Verrucous MF
Waistband MF
Zosteriform MF

beneficial in patients with MF and Sézary syndrome.[8,9] The incidence of *S. aureus* in MF lesions has been reported as 17.0/100 patient-years, whereas cutaneous herpes simplex and herpes zoster virus infections occurred at a combined rate of 3.8/100 patient-years.[10]

Chronic dermatitis has also been linked to the evolution of MF.[11] The distinct entity of "waistband dermatitis" and documented cases of rubber and elastic allergic contact dermatitis abound in the medical literature.[12] A particular type of waistband dermatitis known as "bleached rubber syndrome" only occurs after an elastic waistband has undergone whitening with bleach during the laundering process.[12] Elastic is in the appropriate location to initiate waistband MF, but no specific antigen has yet to be identified as the cause of MF.[13] Additionally, when patient 1 stopped using his athletic pads, his waistband MF lesions improved, suggesting that perhaps there was frequent contact with some antigenic stimulation on the football pads. The literature supports a multifactorial process in which antigenic stimulation produces clonal T cells that acquire mutations, which may explain why MF lesions vary so greatly among patients.[14]

CONCLUSIONS

Our report is the first to describe a variant of stage I MF that we call "waistband MF," which manifests as skin lesions limited to the waistband area. Patients with waistband MF may be misdiagnosed with other cutaneous disorders such as chronic eczema, contact dermatitis, fungal infection, pressure urticaria, viral exanthema, guttate psoriasis, and parapsoriasis. It is possible that antigenic stimulation from elastic or textiles or chronic irritation may play a role in initiating waistband MF. Thus, clinical differential diagnosis and workup of an eczematous lesion in the waistband area should include an evaluation for MF. Physicians should have a high index of suspicion of MF when a chronic dermatitis is present in the waistband area and obtain a biopsy of the lesions with the patient off topical steroids.

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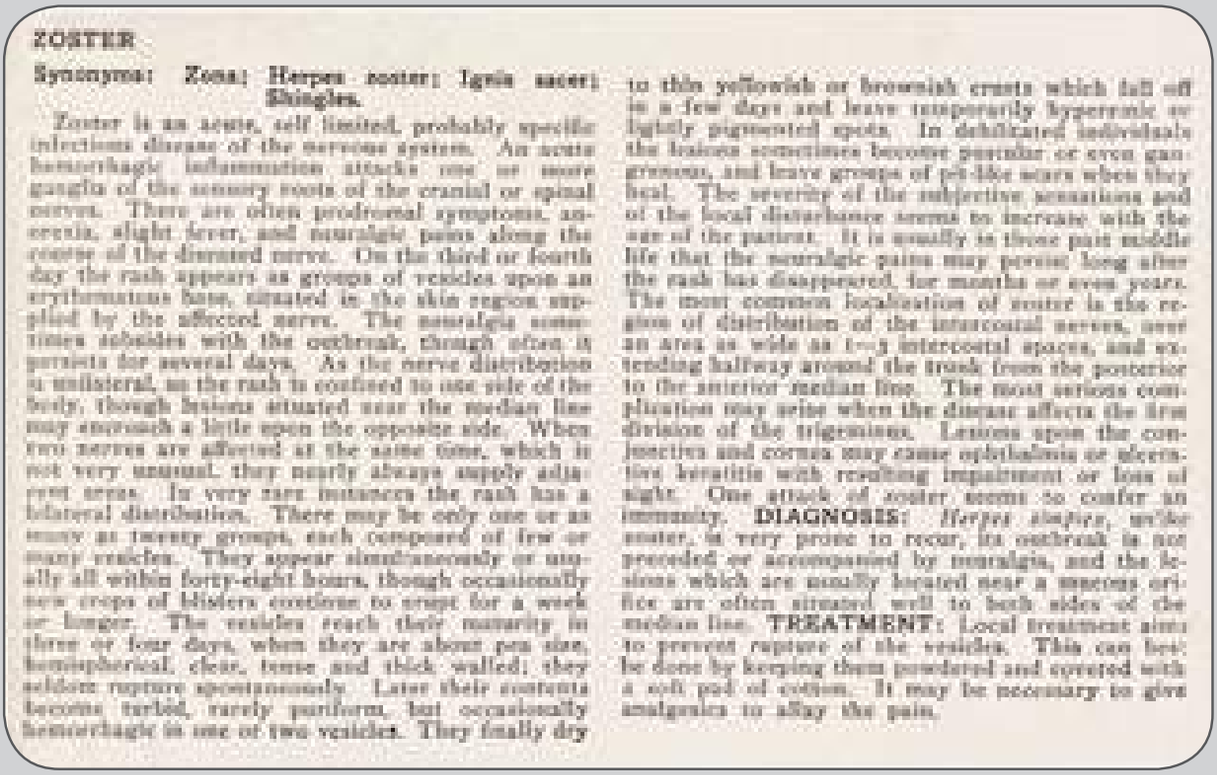
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HISTORICAL DIAGNOSIS AND TREATMENT: ZOSTER

(Continued from page 309)



ZOSTER

Synonyms: Zona; Herpes zoster; Ignis sacer; Shingles.

Zoster is an acute, self limited, probably specific infectious disease of the nervous system. An acute hemorrhagic inflammation attacks one or more ganglia of the sensory roots of the cranial or spinal nerves. There are often prodromal symptoms, anorexia, slight fever, and neuralgic pains along the course of the diseased nerve. On the third or fourth day the rash appears as groups of vesicles upon an erythematous base, situated in the skin region supplied by the affected nerve. The neuralgia sometimes subsides with the outbreak, though often it persists for several days. As the nerve distribution is unilateral, as the rash is confined to one side of the body, though lesions situated near the median line may encroach a little upon the opposite side. When two nerves are affected at the same time, which is not very unusual, they nearly always supply adjacent areas. In very rare instances the rash has a bilateral distribution. There may be only one or as many as twenty groups, each composed of few or many vesicles. They appear simultaneously or usually all within forty-eight hours, though occasionally new crops of blisters continue to erupt for a week or longer. The vesicles reach their maturity in three or four days, when they are about pea size, hemispherical, clear, tense and thick walled; they seldom rupture spontaneously. Later their contents become turbid, rarely purriform, but occasionally hemorrhagic in one or two vesicles. They finally dry to thin yellowish or brownish crusts which fall off in a few days and leave temporarily hyperemic or lightly pigmented spots. In debilitated individuals the lesions sometimes become pustular or even gangrenous, and leave groups of pit-like scars when they heal. The severity of the subjective sensations and of the local disturbance seems to increase with the age of the patient. It is usually in those past middle life that the neuralgic pains may persist long after the rash has disappeared, for months or even years. The most common localization of zoster is the region of distribution of the intercostal nerves, over an area as wide as two intercostal spaces, and extending halfway around the trunk from the posterior to the anterior median line. The most serious complication may arise when the disease affects the first division of the trigeminus. Lesions upon the conjunctiva and cornea may cause ophthalmia or ulcerative keratitis with resulting impairment or loss of sight. One attack of zoster seems to confer an immunity. **DIAGNOSIS:** *Herpes simplex*, unlike zoster, is very prone to recur, its outbreak is not preceded or accompanied by neuralgia, and the lesions which are usually located near a mucous orifice are often situated well to both sides of the median line. **TREATMENT:** Local treatment aims to prevent rupture of the vesicles. This can best be done by keeping them powdered and covered with a soft pad of cotton. It may be necessary to give analgesics to allay the pain.

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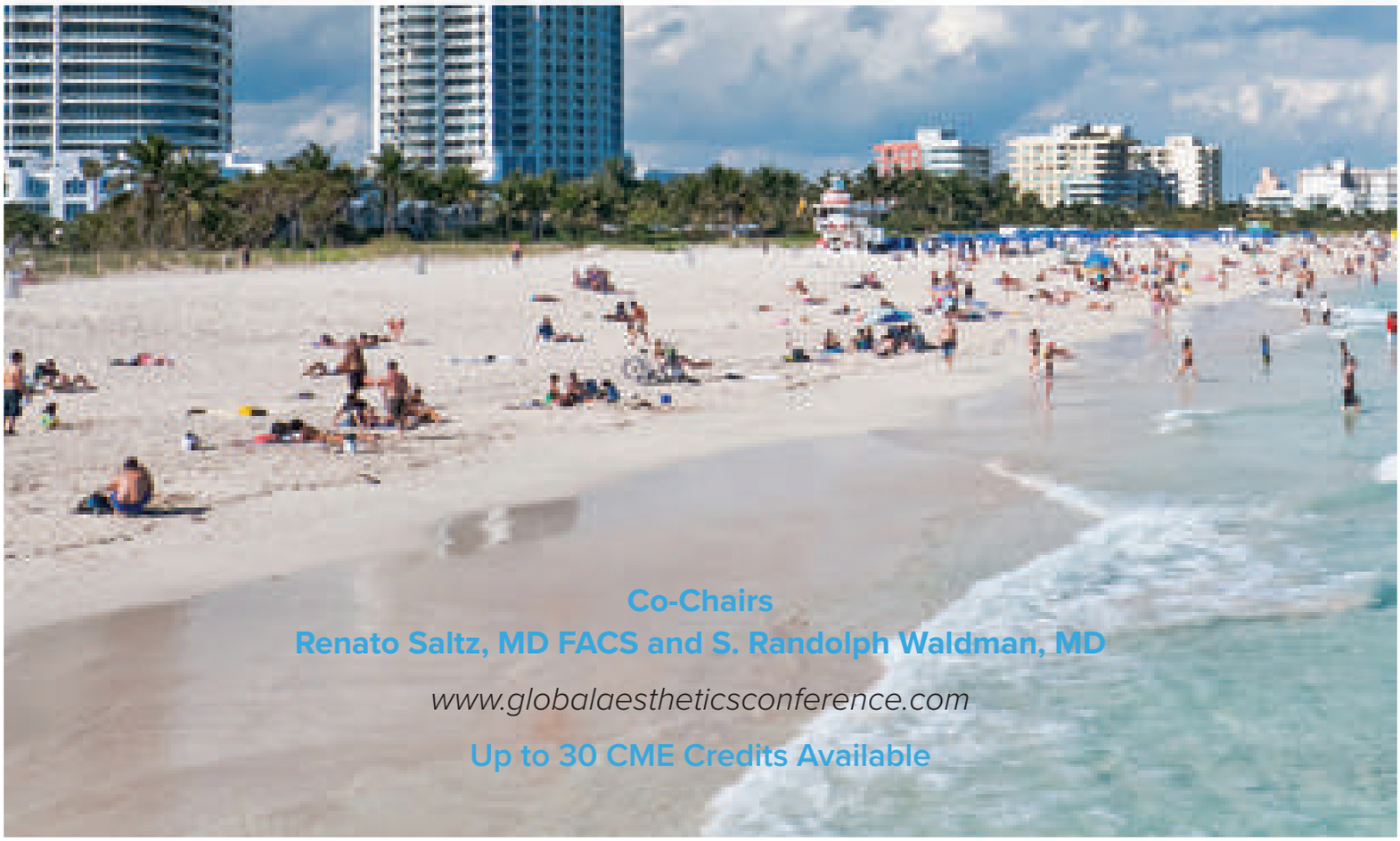
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CASE STUDY

Nodular Demodicosis in a Pregnant Woman Treated with Oral Ivermectin and Metronidazole

Andrew Krispinsky, MD;[1] Matthew Zirwas, MD[2]

A 32-year-old woman presented at 12 weeks' gestation with a severe nodulopustular reaction involving the central region of the forehead and the right cheek (Figures 1 and 2). This had progressively worsened over a several-week period despite use of topical metronidazole. A *Demodex* preparation revealed numerous *Demodex* mites from each pustule that was sampled. Based on the clinical findings and the positive *Demodex* preparations, the woman was diagnosed with nodular demodicosis. (*SKINmed*. 2019;17:334–336)

Four weeks of topical ivermectin was another treatment option, but because of concern for permanent, disfiguring scarring without rapid, effective therapy, a decision was made, after a thorough review of the literature regarding risks during pregnancy, to begin a course of systemic therapy. Treatment consisted of oral ivermectin at 1 mg/10 lb (4.5 kg) of body weight given once and then repeated in a week, in combination with oral metronidazole at a dose of 250 mg three times a day for 14 days, with the first dose taken at the same time as the first dose of ivermectin. The lesions rapidly cleared and resolved without scarring, and the pregnancy progressed without complication (Figures 3 and 4).



Figure 1. Erythematous papules, nodules, and plaques in a pregnant woman. (Courtesy of Matthew Zirwas, MD.)

DISCUSSION

This case is important for two reasons. First, it is a dramatic example of the high level of effectiveness of the combination of oral ivermectin with oral metronidazole. This has been conclusively demonstrated to be the most effective therapy for demodicosis, and one of the authors has had reliable success with it hundreds of times over several years in cases of demodicosis that failed therapy with various combinations therapies.[1] Other documented regimens include oral tetracyclines alone, oral metronidazole alone, oral ivermectin alone, topical metronidazole alone, topical ivermectin alone, and combination therapy with topical ivermectin and topical metronidazole. Second, this case demonstrates the safe use during pregnancy of systemic metronidazole and ivermectin—two medications that are classified as potentially harmful during pregnancy despite a wealth of data showing high levels of safety.

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Figure 2. Nodulocystic lesions on the right cheek. A positive *Demodex* preparation from these confirmed the diagnosis of demodicosis. (Courtesy of Matthew Zirwas, MD.)



Figure 3. Minimal erythema remained after 14 days of systemic ivermectin and metronidazole. (Courtesy of Matthew Zirwas, MD.)

Demodicosis affects the pilosebaceous units of primarily the head and neck, and is caused by the mite *Demodex folliculorum* or *Demodex brevis*. It is one of the many microorganisms present on the surface of human skin, and is likely transmitted from mother to infant during breastfeeding, and through skin-to-skin contact throughout life, with prevalence highest during the 5th and 6th decades.[2]

Most individuals do not exhibit clinical manifestations, and it is, at this time, poorly understood why certain patients are predisposed to developing symptoms. It has been proposed that immunosuppressed patients are at greater risk, but a prospective study showed that only 3% of 115 patients with demodicosis had a known immunodeficiency.[3] Although immunosuppression was not the case in our patient, it is known that the immune system is altered in pregnancy. One notable change is a reduction in cell-mediated immunity and increased susceptibility to skin infections.[4] Much like the increased prevalence of scabies in pregnant patients, it is possible that this alteration led to increased colonization of *Demodex* mites that resulted in our patient's extensive disease.

Our patient presented with primary demodicosis, which must meet the following diagnostic criteria: (1) absence of preexisting/concurrent inflammatory dermatoses; (2) abnormal increase in mite colonization; and (3) resolution of disease after treatment with topical or systemic acaricides/arachnicides.[1,5] It usually involves the follicles of the face (typically periorificial areas), is asymmetrical in distribution, and is asymptomatic or mildly pruritic.[6] Secondary demodicosis occurs in patients with other dermatologic diagnoses or systemic disease.[6]

Three clinical variants of primary demodicosis have been described according to gross appearance and extent of disease, but a consensus nomenclature has not yet been adopted. A classification system has been proposed to clarify a confusing diagnosis. Spiniculate demodicosis describes the most benign form of whitish/yellow spiky changes involving sebaceous hair follicles and minimal erythema.[6] Papulopustular demodicosis manifests with papulopustules involving mostly the face, with significant inflammation.[6] Nodulocystic/conglobate demodicosis is the

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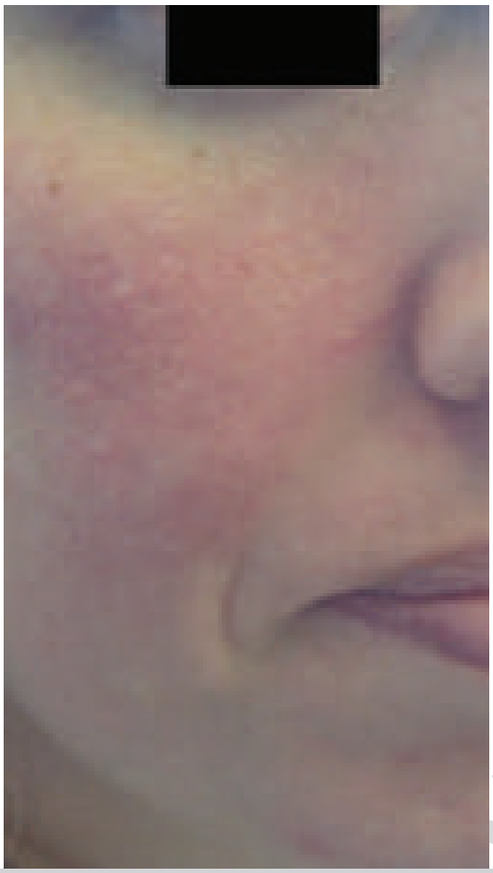


Figure 4. Resolution of nodulocystic lesions without scarring. (Courtesy of Matthew Zirwas, MD.)

result of severe *Demodex* infiltration of follicles resulting in an intense immune response with pus and suppurative changes.[6]

Given the extensive nodular form in our patient, the decision was made for systemic therapy despite her pregnant status. The combined oral therapy of metronidazole and ivermectin has not been widely studied in pregnant subjects to date. Metronidazole is, however, used frequently to treat obstetric patients with bacterial vaginosis and trichomoniasis due to the risk for adverse outcomes if these entities remain untreated.[7] A review of 13 studies showed there was no increased risk for preterm birth or birth defects.[8] Use in a large cohort of first-trimester women showed no increased risk for congenital abnormalities.[9]

Ivermectin has typically been avoided in pregnant patients due to a lack of studies on its teratogenicity. It is used frequently in under developed countries to treat parasitic infections such as filariasis and onchocerciasis. Multiple studies have been performed to assess efficacy and adverse events in pregnant patients in these populations. A retrospective analysis in Ghana and an open-label randomized trial in Uganda found no evidence of increased risk for spontaneous abortion or congenital malformation.[10,11]

CONCLUSIONS

Our case is one example of successful treatment of demodicosis in a pregnant patient with systemic ivermectin and metronidazole, and we believe it is the first of its kind reported in the literature. Because the *Demodex* mite's role in human disease is still not widely accepted among dermatologists, we feel this case provides evidence to further support its pathogenicity. More extensive research is needed, however, to provide statistical significance of this regimen's efficacy and safety among pregnant women.

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CASE STUDY

Chronic Eroded Perianal Plaque in a Patient with Limited Systemic Scleroderma

Fernando Gruber Velasco, BA;[1] Jason C. Sluzevich, MD[2]

A 58-year-old African-American woman presented with a variably painful perianal eruption for 5 years (Figure 1). Prior treatment with topical zinc oxide, oral fluconazole, and Amoxicillin/clavulanic acid resulted in no improvement. She denied chronic diarrhea or cutaneous blistering. Past medical history included limited scleroderma and autoimmune hemolytic anemia treated with daily azathioprine; however, the eruption preceded iatrogenic immunosuppression. Physical examination revealed a well-defined glistening red, ovoid focally eroded plaque involving the intergluteal cleft. The vulva was uninvolved. Oral mucosa was also clear. (*SKINmed.* 2019;17:338–339)

A 3-mm punch biopsy revealed a diffuse dermal plasmacytic inflammation with mild edema and focal epidermal spongiosis. Kappa/lambda immunostaining was polytypic (Figure 2). Gomori Methenamine-Silver, Ziehl–Neelsen, and Gram stains were negative. Polymerase chain reaction assessment for herpes simplex virus and varicella zoster virus was also negative. Swab bacterial cultures were similarly negative. Syphilis antibodies, serum protein electrophoresis, and serum free lights chains were all unremarkable.



Figure 1. Well-defined, bright red, smooth, irregular, focally eroded well-defined perianal plaque. An up-close view of the characteristic glistening appearance reminiscent of a chronic granulation tissue response.

DISCUSSION

Plasma cell mucositis (PCM) is an uncommon inflammatory disorder prototypically involving the oral mucosa and is

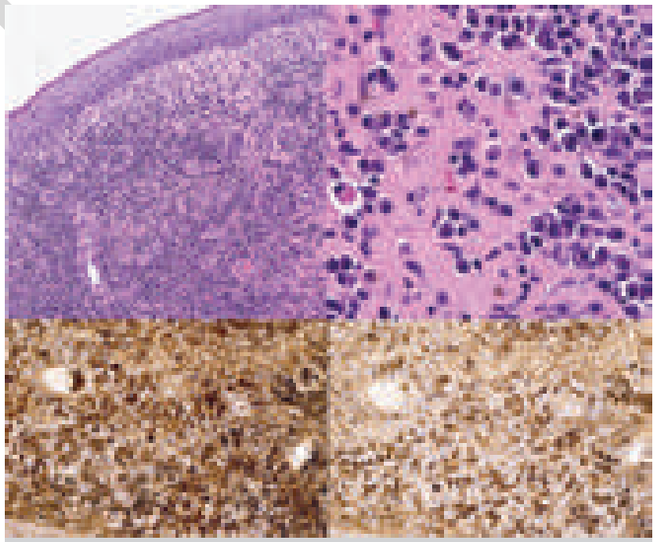


Figure 2. Mild focal spongiosis, dermal edema, and diffuse plasma cell inflammation. Russel bodies are present. The plasma cell infiltrate is polytypic. Hematoxylin and eosin stain; magnification [upper left] × 100; [upper right] × 400. Immunohistochemistry; magnification × 200. Kappa [lower left]; Lambda [lower right].

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histologically characterized by a diffuse plasma cell inflammation.[1] Anogenital involvement is rare and often underrecognized, especially in the setting of exclusive perianal involvement.[2,3]

We report a case of perianal PCM in a patient with scleroderma on chronic immunosuppression presenting as a focally eroded glistening red plaque. The clinical differential included chronic HSV/VZV, secondary syphilis, mucous membrane pemphigoid, cutaneous Crohn's disease, and extra-mammary Paget's disease which all can be confidently discriminated between with routine histopathology.

Most presentations of PCM are idiopathic but may be seen in the setting of autoimmune hepatitis, IgG4 disease, and inflammatory bowel disorders.[4] The exact pathophysiological mechanism leading to chronic plasma cell rich tissue inflammation is unknown, but persistent antigenic stimulation or other indirect form of plasma activation has been postulated.[5]

An association between PCM and scleroderma, to our knowledge, has not been previously described. Patients with scleroderma are known, however, to have plasma infiltrates in association with early tissue sclerosis as well as systemic elevation of IL-6 which has direct maturative and stimulative effects on plasma cells and may have been facultative to the presentation seen in this case.[6]

Treatment of PCM is frequently refractory. Reported treatments include topical class I corticosteroids and topical calcineurin inhibitors, as well as intralesional triamcinolone acetonide 1 mg/cc injections.[4,7] The patient in this case was started on clobetasol 0.05% ointment in combination with acetic acid 0.025% soaks daily with significant improvement after 8 weeks.

CONCLUSIONS

PCM should be considered in the differential of chronic inflammatory disorders involving any mucosal site. Characteristic clinical features include glistening red inflammatory plaques with variable degrees of erosion and a relative lack of pruritus in comparison with other intergluteal eruptions. Routine skin biopsies are diagnostic.

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Letters from Botswana: Diagnostic Challenges of Deep Fungal Infections

Olaf Rodriguez, MD;[1] Karen Mosojane, MBBS;[2] Lawrence Kwape, MBBS;[2] Rahul Diamari, MD;[2] Joseph N. Jarvis, MD;[3,4,5] Karolyn A. Wanat, MD;[6] Carrie Kovarik, MD;[1] Victoria Williams, MD[1,2,3]

To the Editor:

A 50-year-old HIV-positive man presented to the dermatology clinic with a 9-month history of progressive skin lesions. He had started antiretroviral therapy 1 year previously with a CD4 count of 150 cells/mm^3.

Physical examination revealed crusted plaques with erosions on the central area of the face, trunk, and extremities. There was edema encompassing the entire central area of the face, with madarosis and a flattened nasal bridge. Along the lateral aspects of the face and forehead, there were annular violaceous edematous plaques with papulovesicles along the forehead (Figure 1A). There were no enlarged nerves, anesthetic skin lesions, or history of neuritis. The patient reported a nonproductive cough and weight loss but denied other systemic symptoms.

The initial differential diagnoses included discoid lupus erythematosus with bacterial or herpesvirus superinfection, a discoid lupus erythematosus–associated immune reconstitution inflammatory syndrome reaction with superinfection, deep fungal infection (DFI), cutaneous tuberculosis, syphilis, and, less likely, leprosy. His medications included efavirenz/emtricitabine/tenofovir and dapsone. Treatment was initiated with acyclovir, doxycycline, and dilute vinegar soaks.

Bacterial tissue culture was positive for methicillin-sensitive *Staphylococcus aureus* (MSSA) and *Acinetobacter* spp. Fungal culture and an acid-fast bacilli smear were negative. Histopathology revealed superficial and deep perivascular and perineural lymphoplasmacytic infiltrate with histiocytes and scattered eosinophils. Periodic acid Schiff (PAS) staining was negative. Ziehl-Neelsen



Figure 1. (A) Initial presentation showing severe facial edema, crusted erosions across the midface, and clusters of violaceous papulovesicles across the forehead. (B) Two-month follow-up showing crusted ulcerations across the face, chest, arms, and hands, in addition to increasing weight loss. (C) Three-month follow-up showing confluent verrucous crusted plaques encompassing nearly the entire face. (D) Fourth day of hospitalization showing severe edema and thick yellow-brown verrucous crusted plaques with serous drainage, caused by superinfection. (E) Third week of admission, showing decreased edema, resolution of crusting, and healing of underlying eroded plaques. (F) Six weeks after discharge, showing complete healing with residual hypopigmentation and areas of keloidal scarring.

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staining could not be performed because reagents were out of stock. Normal studies included rapid plasma reagin, complete blood count, renal function testing, liver function testing, and chest radiograph. A sputum acid-fast bacilli test was ordered but not completed.

During follow-up over the next 2 months, there was little change clinically (Figure 1B). Repeat rapid plasma reagin tests including serial dilution for the prozone effect were negative. Repeat punch biopsies of the forehead and arm revealed a lichenoid lymphoplasmacytic infiltrate that extended into the deep dermis, with ruptured folliculitis, which favored syphilis. Bacterial tissue culture was positive for MSSA, and fungal culture grew a contaminant and could not be interpreted. During this time, the patient was treated with ciprofloxacin, cotrimoxazole, erythromycin, intramuscular penicillin G, and acyclovir without improvement.

Special stains from the repeat biopsies were available 6 weeks later. PAS findings was negative. Ziehl-Neelsen staining was reported positive for a few bacilli by one pathologist, but three other reviewing pathologists described it as negative. A trial of multidrug therapy with clofazamine, dapsone, and rifampicin was initiated.

At 3-month follow-up, the patient appeared significantly worse, with increased ulceration, cough, and severe dyspnea (Figure 1C). Repeat biopsy was performed, taking the sample from the lateral aspect of the forehead. Working diagnoses now favored a DFI or leprosy with an associated lepra reaction. A repeat chest x-ray was read as normal. Due to the patient's rapidly worsening clinical status, unclear diagnosis, and refusal of admission, a trial of prednisone 40 mg daily and fluconazole 200 mg daily was started in an attempt to improve either diagnosis and stabilize him.

At a follow-up 1 week later, the patient was significantly improved, with decreased facial swelling and crusting, resolved cough, and healing lesions on the upper extremities. The overall clinical picture was highly consistent with a DFI with rapid response to fluconazole. Prednisone and multidrug therapy were stopped, and itraconazole 400 mg daily was initiated. Histopathology subsequently revealed pseudoepitheliomatous hyperplasia with neutrophillic abscesses. Ziehl-Neelsen stains were negative. PAS staining highlighted a few round fungal bodies of approximately 8 to 15 μm. Bacterial tissue culture was positive for MSSA. Fungal tissue culture and an acid-fast bacilli smear were negative. The clinical features combined with new histopathology findings were most consistent with a diagnosis of blastomycosis with bacterial superinfection.

The patient was admitted and started on amphotericin B intravenously 5 mg/kg per day. Cotrimoxazole, mupirocin ointment, and vinegar soaks were started to treat bacterial superinfections (Figure 1D). A lumbar puncture was recommended, but the patient declined. After 3 weeks of admission, the overlying crusting and drainage improved (Figure 1E). At week 4, the patient was discharged on itraconazole 200 mg daily. At a 6 week follow-up, the skin lesions were completely healed, with residual hypopigmentation and keloidal scarring (Figure 1F). Itraconazole 200 mg daily was continued, and the patient was continuing to do well at 6-month follow-up.

DISCUSSION

DFIs can cause significant morbidity and mortality, which is compounded when the diagnosis is delayed. Immunocompromized hosts have an increased risk of disseminated disease and higher mortality rates.[1–3] Among DFIs, the most common pathogens to affect HIV-positive patients in neighboring geographic regions are emmonsiosis, histoplasmosis, and sporotrichosis, while blastomycosis has rarely been reported in Southern Africa.[4] A high index of suspicion for DFIs is necessary in HIV-positive patients when they present with chronic skin lesions unresponsive to antibiotics and/or antivirals.[5] Although DFIs can be acquired via traumatic inoculation of fungal elements by foreign material,[6] certain mycoses, such as blastomycosis, most commonly undergo hematogenous dissemination from a primary pulmonary infection.[7]

As demonstrated by this case, the diagnosis of DFIs can be challenging, especially in resource-limited settings. Even when suspected, the specific fungal organism can rarely be confirmed solely on clinical findings because of the significant clinical overlap between DFIs and other infections. Other factors, such as the bacterial superinfection seen in our case, can further obscure the clinical features. Diagnostic testing may include skin scrapings for KOH examination, skin biopsy for histopathologic examination, and fungal culture. Histopathology most commonly shows a nonspecific granulomatous inflammatory pattern that requires special staining with PAS or Grocott methenamine silver for visualization of fungal organisms, although fungal elements can be sparse and difficult to identify.[8] Tissue cultures are valuable for diagnostic confirmation, but fungal culture laboratories are a scare resource in developing countries, and sensitivity of culture is highly variable based on the quality of the laboratory.

When clinical and histopathologic clues support the diagnosis of a DFI, empiric initiation of a systemic antifungal should be considered even when the exact etiologic agent cannot be confirmed. Although this patient initially presented with skin lesions that

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overlapped with various inflammatory and infectious conditions, over time features more consistent with blastomycosis developed; these included well-demarcated verrucous plaques with central disfiguring ulceration in association with a chronic nonproductive cough. PAS-positive organisms that were the correct size for blastomycosis helped confirm the diagnosis.

CONCLUSIONS

Our patient depicts several important clinical lessons and the complexity of care that is found in Botswana. When the availability and reliability of diagnostic testing is limited, finding the correct diagnosis can often be a trial and error process. The clinical examination should lead management decisions, and clinicians should beware of trusting a single result that does not match overall clinical suspicions. Repeat testing and empiric therapy with close follow-up of clinical response are often needed to work through the differential diagnosis and narrow down an etiology. Clinicians should maintain a high suspicion for endemic mycoses in immunocompromized patients and be aware of the highly variable clinical and histologic presentations of blastomycosis and other DFIs.

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Concurrent Lip Chancre and Maculopapular Syphilides in a Patient under Anti-TNFα Therapy

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To the Editor:

A 21-year-old heterosexual man developed an ulcer on the lower lip during the past month. He had a history of severe Crohn's disease beginning one year ago, and this was controlled with azathioprine and infliximab. We observed a crusted indurated painless ulcer on the lower lip (Figure 1) as well as massive cervical lymphadenopathy. There was also a nonpruriginous maculopapular exanthema involving the trunk and extremities previously unnoticed by the patient (Figure 2). Biopsy of the ulcer showed epithelial hyperplasia and a dense inflammatory infiltrate, while the specimen from the arm revealed a lymphohistiocytic infiltrate (Figure 3). Polymerase chain reaction (PCR) was positive for *Treponema pallidum* both in the exudate of the ulcer and of the oropharynx. He had a reactive *Treponema pallidum* particle agglutination assay (TPPA) and a Venereal disease research laboratory test (VDRL) (1:128 dilution). Screening for HIV, hepatitis B and C, and *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in the urine was negative. The patient discontinued infliximab treatment. He was treated with benzathine penicillin G 2.4 million units intramuscular (IM) per week for 3 weeks, with disappearance of the eruption and slow healing of the lip

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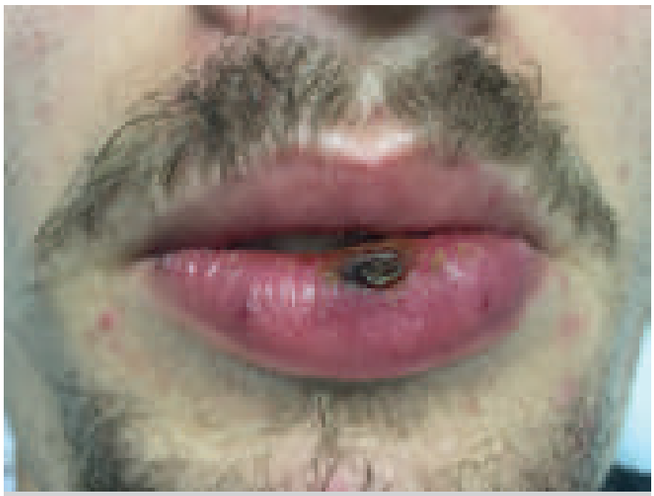


Figure 1. Lip ulcer.



Figure 2. Maculopapular eruption on the hands (a) and foot (b).

ulcer. Throughout clinical evolution, the patient complained of intense headache without ocular symptoms. A lumbar puncture was performed, excluding neurosyphilis. One week after starting treatment with penicillin, there was a significant increase in transaminases and markers of cholestasis, without abnormalities in the abdominal ultrasound. The serologic study revealed markers of acute infection for Epstein–Barr virus (EBV). An oropharyngeal exudate taken for PCR was positive for EBV, and a high EBV load was found in the blood. During follow-up, there was a progressive decrease in the VDRL which became non-reactive after 4 months. A gradual decrease in the EBV load was also found.

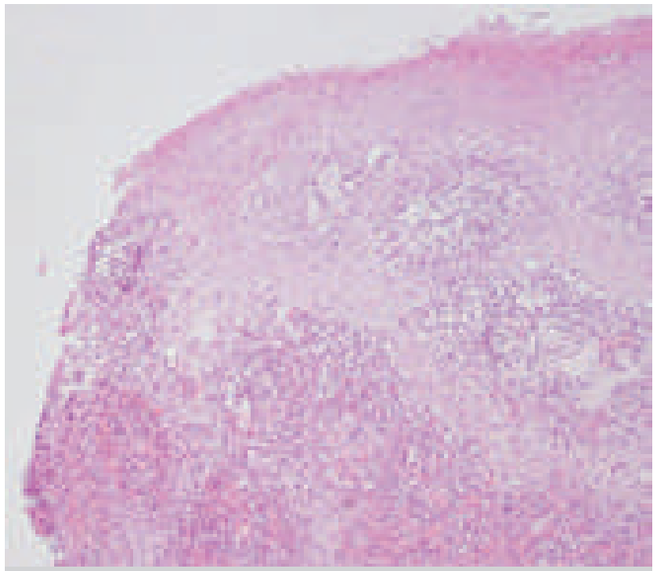


Figure 3. Biopsy of the lip ulcer showing epithelial hyperplasia and a dense inflammatory infiltrate (hematoxylin and eosin ×40).

DISCUSSION

Syphilis is a sexually transmitted disease caused by *Treponema pallidum*.[1] Previous surveillance reports show a recent increasing incidence of the disease among European countries.[2] Finding a lip ulcer in a patient with Crohn's disease is a clinical challenge. Tumor necrosis factor (TNF) inhibitors are widely used in inflammatory bowel disease (IBD), and they pose an increased risk of infections; however, there are no specific recommendations about syphilis in current guidelines.[3–5]

The concurrent primary and secondary stages of syphilis are seldom reported.[6,7] In our case report, we could not ascertain when the eruption appeared, because the patient was unaware of it. A progression of the stages of syphilis in patients under immunomodulatory therapy has been proposed. It would be important to identify the risk factors that induce this unpredictable progression.

There are a few previous reports describing syphilis in patients under treatment with TNF inhibitors.[3–5,8] To the best of our knowledge, this is the first report of a simultaneous primary and secondary syphilis under TNF inhibitor treatment.

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The detected reactivation of EBV could be explained by the unique ability of the human herpes virus to maintain chronic latency in the host, offering protection from immune recognition by limiting viral expression.[9] Biologic agents might unveil an immunologic dysfunction, but thiopurines may be responsible for decreased immunosurveillance of EBV-infected B cells.[10] The hepatic inflammatory markers could be a consequence of viral reactivation, because it was found several days after syphilis treatment. This might be considered as an atypical Jarisch–Herxheimer reaction.

CONCLUSIONS

The introduction of biologic agents in the treatment of IBD has improved the patient's clinical response; yet, the increased risk of infections makes critical close monitoring by both patient and physician. In our opinion, in the setting of a patient under treatment with TNF inhibitors, it is essential to investigate sexual risk behaviors and perform regular screening of sexually transmitted infection (STI).

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Discharging Sinuses over Pre-Sternal Keloids: Quite a Hairy Problem!

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To the Editor:

Keloids are benign fibro-proliferative growths that usually develop in response to trauma or injury to the skin.[1] They are commonly asymptomatic but may be associated with pain, pruritus, and even restriction of joint movement in addition to psychologic distress and impact on quality of life.[2] We report the development of a pilonidal sinus as a novel complication of chest wall keloids, as a result of entrapment of telogen and exogen hairs with resulting secondary inflammatory reaction.

OUR PATIENT

A man in his 50s was referred to the dermatology services for treatment of pre-sternal keloids of 18 months duration. He had previously received intralesional corticosteroids and 5-flurouracil with silicone sheet therapy with minimal success. He was most concerned about the purulent discharging sinuses, which had developed over the last 6 months. With a presumptive diagnosis of atypical mycobacterial infection and bacterial folliculitis, the patient had received multiple courses of antibiotics including

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Figure 1. (a) Multiple discharging sinuses over pre-sternal keloids. Tufts of hair entrapped in the sinuses can be appreciated. (b) Healed surgical site post-radiofrequency ablation without recurrence of sinuses and regrowth or entrapment of hairs.

rifampicin, minocycline, and clarithromycin but without symptomatic improvement.

On examination, extensive keloids were noted over the anterior chest wall. On closer examination, there were multiple pus discharging sinuses surmounting the keloids. Tufts of hair were noticed entrapped in all the sinuses with surrounding inflammation and purulent discharge (Figure 1a). These hair tufts could easily be extracted from the sinus tract with the help of forceps. Extensive microbiologic investigations of the purulent disease and tissue specimens including bacterial and mycobacterial cultures and polymerase chain reaction for typical and atypical mycobacteria were non-productive.

Based on the above findings, we suspect an inflammatory reaction to entrapped telogen hairs within the keloidal tissue. Radiofrequency excision of the keloid along with sinuses and all the hair follicles in the region was performed to prevent the regrowth and trapping of hairs in the future. Histopathology of the excised specimen revealed entrapped terminal hairs traversing the keloids, surrounded by dense inflammatory infiltrate (Figure 2). No pathogenic organisms were noted on special stains, tissue cultures, or polymerase chain reaction. Four months post-surgery, the surgical site had healed with recurrence of keloids without sinuses or entrapment of hair (Figure 1b).

Diagnosis and management of discharging sinuses may be a challenging task for clinicians. These may be associated with a myriad of etiologies including actinomycosis, botryomycosis, and mycetoma or an inflammatory process as in pilonidal sinus or hidradenitis suppurativa. Discharging sinuses over keloids are extremely rare, where atypical mycobacterial infection has been described as a cause following intralesional corticosteroid injections.[3]

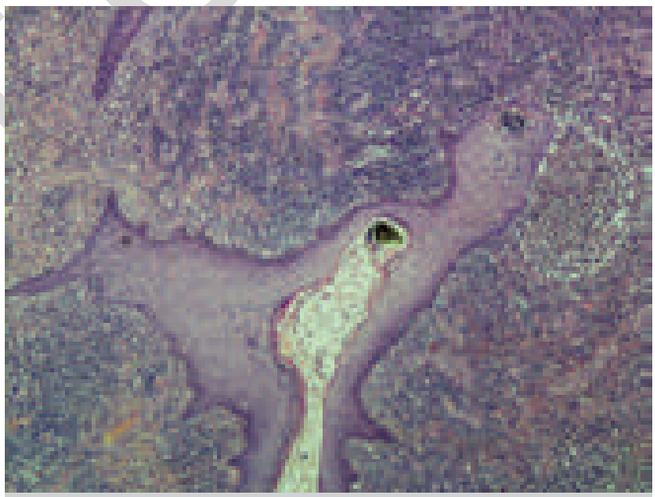


Figure 2. Microphotograph from the edge of sinuses depicting acute or chronic inflammatory reaction against entrapped hair. The infiltrate is comprised predominantly of neutrophils along with histiocytes and lymphocytes (hematoxylin and eosin, 40×).

Hairs have been known to cause cutaneous foreign body reactions leading to the formation of discharging sinuses, as seen commonly in pilonidal sinuses that occur most commonly over sacrococcygeal region and other hair-bearing areas.[4] Pilonidal sinuses in the fingerwebs, especially in the interdigital spaces of occupational hairdressers, are known.[5]

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CONCLUSIONS

Normal hair cycle progresses through the stages of anagen, catagen, and telogen, followed by expulsion of the telogen hair (exogen); however, the fibrous tissue in a keloid may lead to entrapment of growing hairs as well as shed hairs. The entrapped hairs then cause a foreign body reaction leading to inflammation and subsequent sinus formation. In the index case, presence of entrapped hairs in the sinuses, histopathology showing inflammation surrounding entrapped hairs, negative results of microbiologic investigations, and resolution of sinuses on excision of hair follicles suggested a pilonidal sinus as the likely etiology of this unique presentation.

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Topical Calcium Channel Blockers: A Potential New Treatment for Acne

Farnoosh Nozari, MD[1,2]

To the Editor

Acne is a chronic obstructive and inflammatory disorder affecting the pilosebaceous follicles.[1] It is estimated that nearly at least 85% of the population have had this problem at some point in the course of their lifetime.[2]

PATHOPHYSIOLOGY

Acne pathogenesis involves the following factors: excess sebum production by stimulation of sebaceous glands, abnormal keratinization of the follicles leading to comedone formation, *Propionibacterium acnes (P. acnes)* colonization, and inflammation of the follicles.[3] Some aspects of the pathophysiology of acne are detailed below.

Increased sebum production is necessary in the pathogenesis of acne. As sebum passes through the follicular duct, lipases from *P. acnes* hydrolyze a portion of triglycerides into free fatty acids, which cause release of antimicrobial peptides, inflammation, and comedogenesis. There are also increased levels of squalene and squalene oxidase, which promote hypercornification of the follicles.

Oxidized squalene stimulates inflammatory cytokine production. Moreover, it upregulates 5-lipoxygenase (5-LOX), which catalyzes conversion of arachidonic acid to leukotrienes, including leukotriene B4 (LTB4), a potent recruiter of inflammatory cells.

Oxidized squalene also stimulates upregulation of interlukin-1alpha (IL-1α), which can result in hyperkeratinization in the ductal and infundibular regions leading to comedogenesis.

By activating toll-like receptors-2 (TLR2) and TLR4 on keratinocytes and inflammatory cells, *P. acnes* can stimulate TLR-mediated release of cytokines and chemokines. These factors recruit macrophages to the pilosebaceous unit and promote inflammation and rupture of the follicular wall.

TLR-mediated release of cytokines and chemokines induces production of matrix metalloproteinases (MMPs), especially MMP-2, which are involved in tissue destruction and scar formation.[4,5]

POSSIBLE ROLES OF CALCIUM CHANNEL BLOCKERS IN ACNE

Calcium channel blockers (CCBs) are a class of drugs that alter the intracellular calcium (Ca) concentration by modifying Ca influx across cell membranes and affect various intracellular signaling processes.[6]

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Studies have shown that these drugs inhibit fibroblast proliferation and extracellular-matrix protein synthesis. Furthermore, CCBs also have immunomodulatory or disregulatory effects on lymphocytes. They can suppress superoxide generation and phagocytic action of neutrophils and impair mast cell degranulation. On account of these properties, CCBs have been used for the prevention and treatment of various dermatologic diseases, such as erythromelalgia, calcinosis cutis, primary and secondary Raynaud phenomenon, chilblains, chronic anal fissures, keloids, burn scars, and skin flap necrosis;[7] however, no study has yet evaluated the potential roles of CCBs in the treatment of acne.

There are five mechanisms that may explain their potential effectiveness in the treatment of acne:

1. It has been shown that some CCBs such as verapamil are capable of suppressing sebum production as a main contributor to the pathogenesis of acne.[8]
2. Calcium influx plays an essential role in 5-lipoxygenase membrane translocation and leukotriene synthesis;[9] therefore, CCBs may be able to inhibit the production of leukotrienes and subsequent inflammation, as one of the major triggers of acne.[10]
3. Studies have shown that the major enzyme, which is responsible for processing of the precursor of human IL-1α into mature IL-1α, is calcium-activated neutral protease (CANP).[11] CANP is a multi-domain protein comprising a catalytic subunit and a regulatory subunit. This enzyme contains various domains, including a "cysteine protease" domain, two "calmodulin" domains that regulate protease activity, and a membrane-binding domain. The function of the two Ca-binding domains is to activate the repressed protease activity through conformational changes induced by the binding of Ca.[12] Calcium antagonists have the potential to antagonize the calmodulin stimulation of the enzymes;[13] therefore, they might be effective in the treatment of acne.
4. Studies have shown that CCBs, such as nifedipine and verapamil, inhibit the release of cytolytic factors from macrophages and their activation;[14] thus, they might be of value in the treatment of acne.
5. Calcium influx is an important regulator of MMP-2 expression and its subsequent activity.[15] CCBs may play an important role in healing acne scars due to the excessive expression of MMP-2.

CONCLUSIONS

Given its inhibitory effect on sebum production, leukotriene synthesis, upregulation of IL-1α, and MMP-2 expression and also in view of its potential ability to prevent macrophage activation, we theorized that CCBs could be effective against acne. We are conducting further clinical trials on this important subject.

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Karapandzic Flap for the Reconstruction of Defects Following Resection of Squamous Cell Carcinoma of the Lower Lip

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To the Editor:

Most lower lip cancers are squamous cell type and involve the vermillion.[1] Based on the size and localization of the tumor, complete excision and reconstruction are usually the best options. Karapandzic flap is one of the best choices for reconstruction, because it offers repair of defects of up to two-thirds of the lower lip. Our aim is to bring forth the reliable, functional, and cosmetic outcomes of the Karapandzic flap for the reconstruction of large perioral defects of the lower lip.

We present a case series of five patients with surgical defect following the resection of tumors of the lower lip; the reconstruction was performed using the Karapandzic flap. All patients were resected for squamous cell carcinoma. None of the patients presented metastases at the time of diagnosis. All of the interventions were performed under local anesthesia in an outpatient setting; after 24–48 hours, the patients were followed up at the clinic. None of the patients had any adverse events during the surgery, without excessive bleeding or pain. There were no complications; no infection was present in any patient; bleeding was minimum or absent in all the patients; and pain was well controlled. Figures 1 and 2 show the design of the flap and the final result after 1 month. The characteristics of the patients are presented in Table 1.

The lips serve as a pivotal point for facial expression and communication, and they are an important aesthetic component of the face.[2] The Karapandzic flap was first described in 1974[3]; it is characterized as a local rotational flap with preservation of the labial artery and buccal motor nerve branches.[3] It is known to be



Figure 1. Surgical defect and design of the flap.

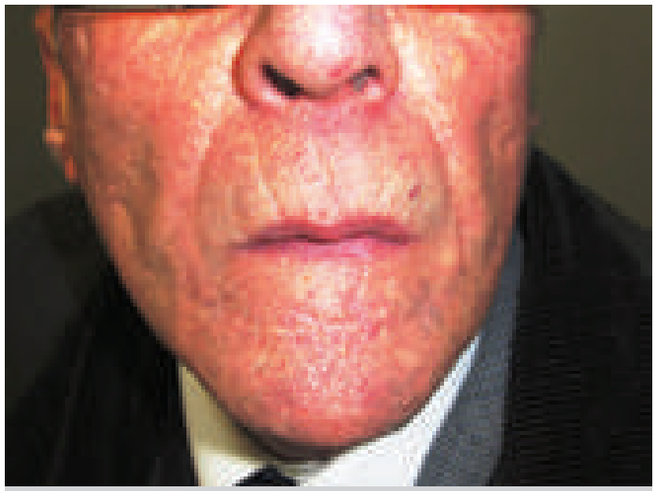


Figure 2. Postoperative status of the lower lip 1 month after surgery.

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Table 1. Characteristics of the Patients

Patient	Age	Sex	Tumor Size (cm.)	Tobacco Use
1	77	Man	1.8	Yes
2	52	Man	1.3	Yes
3	85	Man	2	Yes
4	81	Woman	1.2	No
5	59	Man	1.5	Yes

a one-stage procedure that provides a good oral competence, preserves the function of the lip, and provides a satisfactory aesthetic outcome.[4]

This flap is useful for repairing the defects of one-half to two-thirds of the lower lip.[5] In aged patients, lip redundancy is heightened by the loss of dentition and pre-maxillary bone, which provides excess tissues for reconstruction.[6] This technique allows maintaining the motor function and the sensibility of the lower lip.[7]

The major adverse events of Karapandzic flap include visible scarring and microstomia, which might be corrected with commissurotomy or splints.[2] Of the five patients, only one patient had mild microstomia following the flap, and it was later resolved without any correction with commissurotomy or splints.

All of the five patients in this series had satisfactory functional and aesthetic results.

CONCLUSIONS

Karapandzic flap is a reliable method to reconstruct large perioral defects following tumor resection, with good functional and aesthetic outcomes. This procedure can be safely performed in an outpatient setting under local anesthesia, with diminishing costs, and without inconveniences for the patients.

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BOOK REVIEW

Jennifer L. Parish, MD, Section Editor

Dermatologic Surgery with Radiofrequency: Art of Successful Practice

Deshpande B., *Dermatologic Surgery with Radiofrequency: Art of Successful Practice*. Florida, CRC Press, 2018:138 pages, $59.95.

The medical use of radiofrequency technology dates back to the early 20th century. By converting electricity into thermal energy, this technology can ablate, cut, and manipulate human tissue. Since its introduction, indications for its use have continued to grow and include reduction of incompetent veins, carcinoma ablation, and joint capsule tightening.[1] Within the field of dermatologic surgery, radiofrequency technology allows for the controlled thermal destruction of both dermal and subcutaneous tissues. Deshpande's work on radiofrequency in dermatologic surgery is one of the first and most comprehensive looks at the utility of this technology to date.

Deshpande utilizes years of research, alongside his own personal experience, to navigate readers through the various complexities of radiofrequency surgery. Rather than using conventional, structured checklists often found in such medical books, Deshpande provides a creative and comprehensive manual covering the aggregate from practical surgical suite requirements to complex and detailed operational techniques. The book begins by introducing the basic principles of dermatologic surgery, including patient assessment, necessary equipment, and safety measures. The focus then shifts to the various available surgical modalities with their individual benefits and drawbacks. Only after laying a strong foundation of general dermatologic surgery, including its many nuances and modalities, does the book transition to detailing the utility of radiofrequency within dermatologic surgery. It is at this point, where dozens of indications for radiofrequency therapy are introduced, that the work shines.

From skin tags to basal cell carcinoma (BCC), each indication for surgery with radiofrequency receives a description of the condition at-hand, proper surgical technique, and ideal follow-up care. Deshpande even includes suggestions regarding the radiofrequency device waveform settings, electrode head, and power level for each indication. Throughout this section, he aids visual learners by incorporating hundreds of procedural photos and illustrations. From a photo sequence of a recurrent mole excision to the histologic results of a successful excisional biopsy, the inclusion of such figures provides a valuable, alternative perspective to the information at hand.

The text cumulates with methods to minimize surgical complications and achieve superior aesthetic results. The author addresses obstacles secondary to anesthesia, equipment, and patient noncompliance, along with proposals to minimize each issue. It is here where Deshpande also incorporates surveyed patient data. By doing so, he illuminates the patient perspective of undergoing surgery with radiofrequency, particularly as it pertains to surgical technique, post-operative complications, and aesthetic results. This input captures a dimension of the patient experience rarely seen in such formal works.

This book provides the direction and tools to create a surgical atlas applicable to practitioners worldwide. Although focused on the use of radiofrequency, a significant portion of the book's lessons extends across the general field of dermatologic surgery. Deshpande's extensive insight may empower future physicians to consider the role of such technology within their own clinics. Whether a new provider or seasoned practitioner, this book is a worthwhile addition to any dermatologic library.

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LEVULAN® KERASTICK® (aminolevulinic acid HCl) for Topical Solution, 20%
Initial U.S. approval: 1999

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use LEVULAN KERASTICK safely and effectively. See full prescribing information for LEVULAN KERASTICK.

INDICATIONS AND USAGE

LEVULAN KERASTICK for topical solution, a porphyrin precursor, plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the photodynamic therapy (treatment) of minimally to moderately thick actinic keratoses of the face or scalp, or actinic keratoses of the upper extremities.

DOSAGE AND ADMINISTRATION:

The LEVULAN KERASTICK topical solution 20% is intended for direct application to individual lesions diagnosed as actinic keratoses and not to perilesional skin. This product is not intended for application by patients or unqualified medical personnel. Application should involve lesions on the scalp, face or upper extremities; multiple lesions can be treated within a treatment region, but multiple treatment regions should not be treated simultaneously.

The recommended treatment frequency is one application of the LEVULAN KERASTICK topical solution and one dose of illumination per treatment region per 8-week treatment session. Each individual LEVULAN KERASTICK applicator should be used for only one patient.

LEVULAN KERASTICK photodynamic therapy for actinic keratoses is a two-stage process involving application of the LEVULAN KERASTICK topical solution to the target lesions and then illumination with blue light using the BLU-U Blue Light Photodynamic Therapy Illuminator after 3 hours for upper extremity lesions or after 14-18 hours for face or scalp lesions.

CONTRAINDICATIONS

The LEVULAN KERASTICK for topical solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK.

WARNINGS AND PRECAUTIONS

Transient Amnestic Episodes

Transient amnestic episodes have been reported during postmarketing use of LEVULAN KERASTICK in combination with BLU-U Blue Light Photodynamic Therapy Illuminator. Inform patients and their caregivers that LEVULAN KERASTICK in combination with PDT may cause transient amnestic episodes. Advise them to contact a healthcare provider if the patient develops amnesia after treatment.

Photosensitivity

After LEVULAN KERASTICK topical solution has been applied, the treatment site will become photosensitive and patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) for 40 hours. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Therefore, before exposure to sunlight, patients should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material, and/or a long-sleeved shirt and/or gloves. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK topical solution outside the treatment site to the eye or surrounding skin.

Application of LEVULAN KERASTICK topical solution to perilesional areas of photodamaged skin of the face, scalp or upper extremities may result in photosensitization. Upon exposure to activating light from the BLU-U, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN KERASTICK Photodynamic Therapy. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK topical solution should be used by a qualified health professional to apply drug to no more than 5mm of perilesional skin surrounding the target actinic keratosis lesions. If for any reason the patient cannot return for blue light treatment during the prescribed period after applying LEVULAN KERASTICK topical solution, the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

Irritation

The LEVULAN KERASTICK topical solution contains alcohol and is intended for topical use only. Irritation may be experienced if this product is applied to eyes or mucous membranes. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion longer than 3 hours.

Coagulation Defects

The LEVULAN KERASTICK for topical solution has not been tested on patients with inherited or acquired coagulation defects.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rate 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.

In clinical trials, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK photodynamic therapy.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK photodynamic therapy (PDT) was observed in all clinical trials for actinic keratoses treatment.

Local skin reactions at the application site were observed in 99% of subjects treated with LEVULAN KERASTICK topical solution and BLU-U Blue Light Photodynamic Therapy Illuminator. The most common local adverse reactions (incidence ≥ 10%) were application site stinging/burning, erythema, edema, scaling/crusting, hypo/hyperpigmentation, itching, erosion, oozing/vesiculation/crusting, dryness.

In the trials for face and scalp lesions, severe stinging and/or burning at one or more lesions during light treatment was reported by at least 50% of subjects. Severe stinging and/or burning also occurred during light treatment in 9% of subjects receiving treatment for upper extremity lesions.

In trials for the face or scalp lesions, 99% of the active treatment group and 79% of the vehicle group experienced erythema shortly after treatment. In the trial for the upper extremity lesions, 99% of LEVULAN KERASTICK topical solution treatment group and 52% of the vehicle group experienced erythema on visit Days 2-3. Approximately 35% of LEVULAN KERASTICK topical solution group had edema, while edema occurred in <1% of the vehicle group. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy for face or scalp. Edema resolved by 4 weeks and erythema resolved to baseline by 8 weeks for upper extremities. The application of LEVULAN KERASTICK topical solution to perilesional skin resulted in stinging, burning, erythema and edema similar to treated actinic keratosis

Other Localized Cutaneous Adverse Experiences: Table 1 depicts the incidence and severity of cutaneous adverse events in trials for the face and scalp. Table 2 depicts the percentage of subjects with cutaneous adverse reactions by the most severe grade reported in course of the trial for the upper extremity lesions.

TABLE 1 Post-PDT Cutaneous Adverse Events – ALA-018/ALA-019 For the Face and Scalp

	FACE				SCALP			
	LEVULAN KERASTICK Topical Solution + PDT (n=139)		Vehicle + PDT (n=41)		LEVULAN KERASTICK Topical Solution + PDT (n=42)		Vehicle + PDT (n=21)	
Degree of Severity	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe
Scaling/Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyper-pigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0%

TABLE 2 Percentage of Subjects with Cutaneous Adverse Reactions by the Most Severe Grade Reported Post-Baseline – CP0108 For Upper Extremities

	LEVULAN KERASTICK Topical Solution + PDT (N=135)			Vehicle + PDT (N=134)		
Degree of Severity	Minimal/ Mild	Moderate/ Severe	Total	Minimal/ Mild	Moderate/ Severe	Total
Edema	51%	4%	56%	7%	1%	8%
Erythema	35%	65%	100%	63%	12%	75%
Hyper-pigmentation	64%	9%	73%	57%	10%	66%
Hypo-pigmentation	46%	4%	50%	50%	5%	55%
Oozing/Vesiculation/ Crusting	36%	5%	41%	8%	2%	10%
Scaling and Dryness	65%	22%	87%	58%	7%	64%
Stinging/Burning	23%	73%	96%	23%	0%	23%

In the trial for upper extremity lesions, itching and scabbing occurred in 8% and 4%, respectively, of the subjects in the LEVULAN KERASTICK photodynamic therapy group. No subjects in the vehicle group reported itching or scabbing.

Common (>2%, <10%) local cutaneous adverse reactions for face, scalp and upper extremities in the LEVULAN KERASTICK topical solution group included wheal, scabbing, pustules, ulceration, bleeding, tenderness and dysesthesia.

Uncommon (<2%) local cutaneous adverse reactions for face, scalp and upper extremities in the LEVULAN KERASTICK topical solution group were flaking, pain, peeling, perilesional pruritic rash, excoriation and blistering.

Common (>2%, <10%) adverse reactions not limited to the application site for upper extremities and occurring more frequently in the LEVULAN KERASTICK topical solution group than in the vehicle group were sinusitis, squamous cell carcinoma, and squamous cell carcinoma of skin.

Postmarketing experience:

The following adverse reactions have been reported during post-approval use of LEVULAN KERASTICK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Nervous system disorders: transient amnestic episodes

DRUG INTERACTIONS

There have been no formal studies of the interaction of LEVULAN KERASTICK topical solution with any other drugs, and no drug-specific interactions were noted during any of the controlled clinical trials. It is, however, possible that concomitant use of other known photosensitizing agents such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with LEVULAN KERASTICK topical solution.

USE IN SPECIFIC POPULATIONS:

Pregnancy

Limited available data with LEVULAN KERASTICK topical solution use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. Animal developmental toxicology studies were not conducted with aminolevulinic acid. LEVULAN KERASTICK solution has low systemic absorption following topical administration, and the risk of maternal use resulting in fetal exposure to the drug is unknown.

Lactation

There are no data on the presence of LEVULAN KERASTICK topical solution in either human or animal milk, the effects on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LEVULAN KERASTICK topical solution and any potential adverse effects on the breastfeeding child from LEVULAN KERASTICK topical solution or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness in pediatric patients below the age of 18 have not been established. Actinic keratosis is not a disease generally seen in the pediatric population.

Geriatric Use

Of the 512 subjects in Phase 3 clinical trials of LEVULAN KERASTICK topical solution, 63% (321/512) were 65 years old and over, while 24% (123/512) were 75 years old and over. No overall differences in safety or substantial differences in effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

In the event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours after ingestion. The consequences of exceeding the recommended topical dosage are unknown. There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK topical solution application.

PATIENT COUNSELING

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Transient Amnestic Episodes

Transient episodes of amnesia have been reported with LEVULAN KERASTICK in combination with BLU-U Blue Light Photodynamic Therapy Illuminator. Advise patients and their families or caregivers to contact their healthcare provider if memory impairment, confusion, or disorientation is observed.

Photosensitivity

Advise patients that after LEVULAN KERASTICK topical solution has been applied, the treatment site will become photosensitive and that they should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) for 40 hours. Advise patients to protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material, and/or a long-sleeved shirt and/or gloves. Advise patients sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK topical solution outside the treatment site to the eye or surrounding skin.

If for any reason the patient cannot return for blue light treatment during the prescribed period after applying LEVULAN KERASTICK topical solution, advise patients to call the doctor. Advise patient to continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. Advise patients to avoid certain medications that may enhance the phototoxic reaction to PDT.

Common Adverse Reactions

Inform patients that treatment with LEVULAN KERASTICK topical solution plus BLU-U Blue Light Photodynamic Therapy Illuminator may result in sensitivity to light, skin irritation and local skin reactions including erythema, edema, stinging/burning, scaling, crusting, oozing, vesiculation, wheal, scabbing, pustules, ulceration, itching, erosion, hypo/hyperpigmentation, bleeding, tenderness, dysesthesia, and dryness.

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.

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SUN DERMATOLOGY

PROOF



TRUSTED IN MORE THAN 3 MILLION PATIENT TREATMENTS NATIONWIDE[2]

The proven in-office therapy[3], LEVULAN KERASTICK + BLU-U provides:

DEMONSTRATED EFFICACY + DISTINCTIVE DELIVERY + DEDICATED SUPPORT TEAM

DO NOT

Important Safety Information

LEVULAN® KERASTICK® (aminolevulinic acid HCl) for topical solution, 20%, plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp, or actinic keratosis of the upper extremities.

Contraindicated in patients with cutaneous photosensitivity at wavelengths of 400–450 nm, porphyria, known allergies to porphyrins, and/or known sensitivity to any of the components of the LEVULAN KERASTICK. LEVULAN KERASTICK topical solution has not been tested on patients with inherited or acquired coagulation defects.

Transient amnestic episodes have been reported during postmarketing use of LEVULAN KERASTICK in combination with BLU-U Blue Light Photodynamic Therapy Illuminator. Inform patients and their caregivers that LEVULAN KERASTICK in combination with PDT may cause transient amnestic episodes. Advise patients to contact a healthcare provider if amnesia develops after treatment. Do not apply to the eyes or to mucous membranes as irritation may be experienced. Excessive irritation may occur if LEVULAN KERASTICK is applied under occlusion for longer than 3 hours. Occlusion is used only in the treatment of lesions of the upper extremities. LEVULAN KERASTICK topical solution should be applied by a qualified health professional to no more than 5 mm of perilesional skin surrounding each target lesion. During light treatment, both patients and medical personnel should be provided with blue blocking protective eyewear.

Patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light for 40 hours after LEVULAN KERASTICK topical solution application. Advise patients to protect treated areas with light-opaque clothing, such as long sleeves or a hat. Sunscreens will not protect the patient against photosensitivity reactions caused by visible light.

Concomitant use of other known photosensitizing agents such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides, and tetracyclines might increase the photosensitivity reaction.

The most common local adverse reactions (incidence ≥ 10%) were erythema, edema, stinging/burning, scaling/crusting, itching, erosion, hypo/hyperpigmentation, oozing/vesiculation/crusting, scaling, and dryness. In clinical trials, severe stinging and/or burning was reported by at least 50% of face and scalp patients and 9% of upper extremity patients at some time during treatment.

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

References: 1. Symphony Health. Actinic Keratosis Total Patient Share. June 2018. **2.** Data on file, Sun Pharma. **3.** LEVULAN KERASTICK (Prescribing Information). Sun Pharma; April 2018.

SUN DERMATOLOGY

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