Vesiculobullous Syphilis: A Case Involving an Unusual Cutaneous Manifestation of Secondary Syphilis

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ABSTRACT

The recent resurgence of syphilis mandates that clinicians maintain a heightened suspicion for *Treponema* infection, and that they be aware of the variety of cutaneous presentations that may mimic eczema, psoriasis, drug eruption, erythema multiforme, lichen planus, tinea versicolor, seborrheic dermatitis, mycosis fungoides, or other lichenoid lesions. In this report, we describe an unusual case of secondary syphilis in an adult woman, and briefly review the wide array of syphilitic dermopathy that could present to the foot and ankle surgeon.

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During the past decade, it has come to be generally known that the prevalence of syphilis has increased. This resurgence mandates that clinicians maintain a heightened suspicion for this chameleon of dermopathies. Common cutaneous manifestations include macular, papular, and maculopapular eruptions, but unusual manifestations can also occur. Traditionally, however, vesicular, bullous, and pruritic rashes have been considered less likely to be associated with the diagnosis of secondary syphilis.

In this report, we describe an unusual cutaneous manifestation of secondary syphilis that was initially confused with other more benign dermatoses, and incorrectly treated because of the inaccuracy of the initial diagnosis. Proper treatment was not rendered until serologic screening for syphilis was conducted and an accurate diagnosis was made. In addition to the case report, we review the clinical presentation and diagnosis of primary and secondary syphilis.

Case Report

A 41-year-old African-American woman presented to our clinic with a history of tiny vesicular eruptions on the plantar aspect of her right heel, which, over the course of 2 weeks, had coalesced into a single large, tender, bullous lesion. She had previously been treated with oral cephalexin and topical corticosteroid, neither of which had resolved the rash. She denied systemic symptoms, such as fever, malaise, or any other constitutional abnormality. Her vital signs were also within normal limits, and the physical examination was significant for a large, intact, bulla localized to the plantar aspect of the right foot (Figure 1). The base of the lesion resembled a burn, in that it displayed moist, brightly erythematous tissue with an intact dermis. There was no evidence of necrosis or penetrating lesion beyond the superficial ulceration. The plantar arch and heel were fluctuant, with an overtly palpable air-fluid interface. The perimeter of the lesion was sharply demarcated with an erythematous rim approximately 4 mm in width (Figures 2 and 3). No increased skin temperature gradient was noted in either lower extremity, and numerous small, circular, well-circumscribed areas of keratotic plantar scaling that appeared chronic in nature were noted on the contralateral foot. There were no other skin lesions or palpable or tender inguinal lymphadenopathy affecting either lower extremity. In an effort to refine the diagnosis, we procured approximately 60 cc of serosanguinous aspirate from the bulla and submitted this for laboratory analysis, along with blood for a complete blood count and erythrocyte sedimentation rate (ESR).

Dorsoplantar- and lateral foot–view radiographs (Figures 4 and 5) showed considerable soft tissue swelling along the plantarmedial aspect of the tarsals, and radiolucent contrast suggestive of an air-fluid interface associated with the bulla. The complete blood count and ESR were normal, and the Gram's stain of the fluid was negative for organisms and polymorphonuclear white blood cells. No yeast cells or mycelial elements were noted on the potassium hydroxide preparation, and aerobic bacterial cultures grew coagulase-negative *Staphylococcus* species. Anaerobic, fungal, and acid-fast cultures were negative.

Because of the chronic nature of the eruption and failure of initial therapy to resolve the condition, an infectious diseases consultant was also asked to participate in the evaluation and care of the patient. Based on the infectious diseases consultant's recommendations,

Fig. 1. (A) Photograph of the dorsum of the right foot that is spared of the bizarre vesicular eruption as compared with the arch of the right foot seen in part B. (B) Clinical photograph of the plantar aspect of the right foot showing bullous lesion involving 2/3 of the foot. A sharply demarcated erythematous margin outlining this fluid-filled pouch is easily appreciated. The central aspect of the lesion is mottled with small vesicles that appear to be coalescing. The epidermolysis is so profound that you can appreciate folds of skin that have been undermined within the most distal aspect of the lesion. The fluid:air level creates a 2.5-cm margin within the distal bullous. The area is exquisitely tender; however, it is without calor or edema.

specific serologic tests were obtained and particular concern was expressed for the possibility of syphilis. The rapid plasma reagin (RPR) was positive at 1:32, and the fluorescent treponemal antibody absorption test (FTA-ABS) was also reactive. It is the authors' understanding that most infectious disease specialists rely on the FTA-ABS and RPR to confirm the diagnosis of syphilis. Additional testing can include silver staining and dark field microscopic analyses, which are illustrated herein (Figures 5 and 6).

The patient was treated for secondary syphilis with 2.4 million U of intramuscular benzathine penicillin. She was also encouraged to contact persons with whom she had been sexually active, in order to inform them that they should seek evaluation and treatment as well. Twelve hours after initial dosing, new vesicular eruptions appeared on the sole of the contralateral foot. The following day, however, the lesions on both feet began to regress, and, after 7 days, the original bulla had regressed (Figure 7). Resolution of the lesion progressed until sloughing of the superficial residual keratotic tissue was complete. The patient continued to be seen in the clinic for scheduled follow-up care and the lesion did not recur over the subsequent 4 months, after which the patient was lost to follow-up.

Discussion

It has been postulated that *Treponema pallidum* originally arose from free-living treponemes found in the mud that came to be carried commensally by man (1). Today, 3 treponemes are known to be pathogenic to man, namely: *T. pallidum*, the cause of venereal and nonvenereal syphilis; *T. pertenue*, the cause of yaws; and *T. carateum*, the cause of pinta. In humans, venereal syphilis is worldwide in distribution, whereas the other treponematoses are associated with specific geographical locations and climates (2).

In 1980, 27,206 cases of syphilis were reported in the United States; by 1990, the prevalence increased tremendously, with a total of 52,575 reported cases (3). The increase in reported cases between 1980 and 1990 is directly related to a decrease in federal funding for the prevention of sexually transmitted diseases that was enforced during this period. Regarding primary and secondary syphilis, case reports are on the rise; 6862 cases reported in 2002 and 11466 cases reported in 2007, which corresponds to a change in incidence from 2.4 cases in 100,000 to 3.8 cases in 100,000 respectively, according to the Centers for Disease Control (4). The disease occurs most frequently in adults 20 to 24 years of age, followed by (in order of decreasing incidence) 30- to 34-year-olds, and 15- to 19-year-olds. The male:female ratio is approximately 2:1, with a very high prevalence among homosexual men (4).

Syphilis is transmitted principally through sexual contact, or by means of in utero exposure during the primary and secondary stages. In childbearing women, the untreated condition may affect the fetus regardless of the stage of the disease. A woman with congenital syphilis, however, is not infectious to her fetus unless she has been re-infected with acquired syphilis (3). The chancre of primary syphilis occurs after intimate sexual contact, but has never been reported in association with syphilis contracted after blood transfusion. Interestingly, untreated individuals may be contagious for longer than a 1-year period.

Clinical manifestations of systemic dissemination of *Treponema pallidum* reflect both humoral (B-cell) and cellular (T-cell) inflammatory responses to the spirochetes. The hallmark of the primary stage is a single chancre, although multiple sites of inoculation may

Fig. 2. With the bullous suspended to gravity, the fluid margin is best appreciated and the underlying "meaty"-appearing base of the lesion can be seen. An air-fluid level line can be appreciated as an erythematous band that demarcates the distal aspect of the bullous. The skin without fluid beneath is sealing down to the underlying skin distal to this erythematous band.

Fig. 3. The lesion transilluminated well. Upon aspiration, 60 cc of serous fluid was removed, and, although the lesion was drained completely, it became apparent that the base of the lesion was actively producing more exudate when a small accumulation began to fill in the proximal base of the lesion an hour after aspiration. No malodor or necrotic debris was noted in the thin, serous fluid. Ultimately, the fluid cultures grew coagulase-negative staphylococcus, whereas the PAS and fungal stains of the fluid were negative.

result in multiple primary lesions. Typically, by approximately 3 weeks after exposure (range, 9-90 days), at the site of inoculation, a button-like papule appears, which quickly and painlessly erodes into an ulcer (≤ 2 cm in diameter) with a beefy-red base, and an indurated border, often with surrounding edema. The secondary stage appears weeks to months later, as hematogenous and lymphatic dissemination triggers an immune response. Early secondary syphilis often presents with flu-like symptoms such as headache, malaise, fatigue, nasal and/or lacrimal discharge, sore throat, generalized arthralgia, and/or low-grade fever. An elevated ESR and an increased white blood cell count with absolute lymphocytosis have also been reported in association with secondary syphilis (3). Regional lymph nodes may be enlarged and are generally nontender, and, not uncommonly, the adenopathy may be severe enough to mimic Hodgkin's disease (5). Splenomegaly and, less commonly, hepato-megaly may be present. Rarely, secondary syphilis is associated with hepatitis, meningitis, headache, peripheral neuropathy, deafness, nephritic syndrome, arthritis, iridocyclitis, or periostitis (7). Although a complete review of syphilis and HIV is beyond the scope of this article, it is important to note that concurrent infection with HIV commonly hastens progression to neurosyphilis (8).

The earliest cutaneous manifestation of secondary syphilis occurs concomitantly with the systemic signs. It commonly manifests as a transitory, morbilliform rash on the upper trunk and flexor surfaces of the extremities. The rash is usually painless and occasionally pruritic (6) and may last from several weeks to a year. In Mindel and colleagues' 20-year retrospective study, 40% of syphilitic rashes were macular, 40% maculopapular, and 10% papular (7). None of the cases in that report, however, involved a bullous eruption like the one described in the patient presented in this report. In a review of 105 patients with secondary syphilis, Chapel (6) found that 26.7% of patients were unaware of their mucocutaneous lesions and that 21% had inconspicuous lesions, and approximately 8% of the cutaneous lesions displayed distributions and morphologic features suggestive of other dermatoses, including eczema, psoriasis, drug eruptions, erythema multiforme, mycosis fungoides, and other lichenoid lesions (9). Less common dermal manifestations of secondary syphilis include squamous, pustular, circinate, nummular, and corymbiform eruptions (9). Vesicular lesions, such as those observed in the patient who we described in this report, although rare, have been reported previously (10). It is also interesting to note that the morphology and appearance of the rash differ depending on location, with lesions of the palms and soles being more hyperkeratotic than those elsewhere on the body, and this feature may lead the clinician to mistakenly diagnose the condition as tinea pedis (11). In our patient, an aberrant form of tinea pedis was included in the differential diagnosis, although this was low on the list because of the unusual size of the lesion and its copious fluid production. In areas of thick hair growth, secondary syphilis lesions can be follicular and may cause nonscarring, non-erythematous alopecia of the scalp, beard, and/or eyebrows. Oral lesions typically involve ulcerations at the tip and sides of the tongue (3). An atypical presentation of secondary syphilis, one that involved painful, cyanotic toes with a positive skin biopsy and response to treatment, was reported by Federman et al (12). Intertriginous lesions (condylomata lata) appearing as moist, exophytic, digital web space plaques, combined with perineal lesions, have been described by Rosen and Hwong (13). Still further, secondary syphilis can be accompanied by transient, postinflammatory hyperpigmentation (5, 14), followed by development of a coppery-red maculopapular

Fig. 4. (A) Plain radiographs were negative for osseous defect. (B) An air:fluid level appreciable on the lateral view consistent with the bullous lesion and its fluid contents.
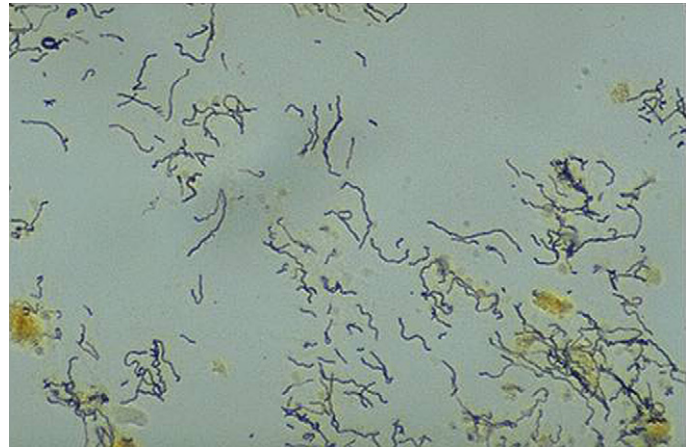

Fig. 5. A microscopic slide of the silver stain for identification of the treponeme of syphilis. Numerous helical bodies can be seen. Note the rare clumps of pigment—remnants of the staining process—about the perimeter. Spirochetes once identified with a silver stain, as seen here, are now elucidated with immune histochemical staining techniques.

of the rash is typically followed by a latent period, and about 25% of patients will develop clinical signs and symptoms of relapse. Of that 25% only 20% (that is, 5% of the total population) may experience as many as 3-relapsing episodes (3).

A provisional diagnosis of secondary syphilis is based on the clinical features and the social history of the patient. Diagnostic testing often includes dark field microscopy, tissue biopsy, and serologic screening. Dark field microscopy identifies the spirochete in exudates from chancres, papulosquamous secondary lesions, condylomata lata, and/or enlarged regional lymph nodes. However, this histologic test requires technical personnel experienced in preparing specimens and a special microscope condenser. The dark field examination will be impaired if an antiseptic, topical antibiotic or even petroleum jelly are present on the specimen, which have been associated with false-negative diagnoses. Biopsy of a lesion is an alternate means of diagnosis, although the histopathology of secondary syphilis mimics many other diseases. In primary and secondary syphilis, the biopsy specimen shows central thinning or ulceration of the epidermis, lymphocyte and plasmacyte

eruption. Late papular lesions may be hypertrophic, lichenoid, or psoriasiform. Of particular interest in regard to the patient who we described in this report, was the distinctive coppery-red discoloration about the periphery of the pedal lesion. Generalized eruptions on glabrous skin of the face, trunk, and extremities may resemble lichen planus, psoriasis, tinea versicolor, or seborrheic dermatitis (3, 6, 14).

Postinflammatory effects in skin can be seen as either hyperpigmentation or depigmentation. Crown of Venus (corona veneris) is a pattern of pigmentary change that develops on the forehead and the frontal and temporal hairlines, reflecting the former distribution of rash. Similar lesions can be found along the neck and chest and are referred to as the collar of Venus and leukoderma colli (3). Resolution
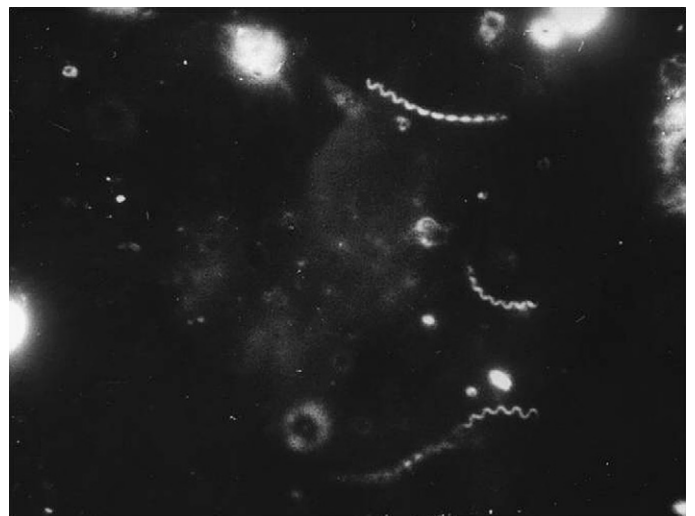

Fig. 6. This dark field microscopy of the immune fluorescence staining technique reveals the pathognomonic helical morphology of the treponemes of secondary syphilis. Although this staining technique is diagnostic, it is rarely used in clinical practice.
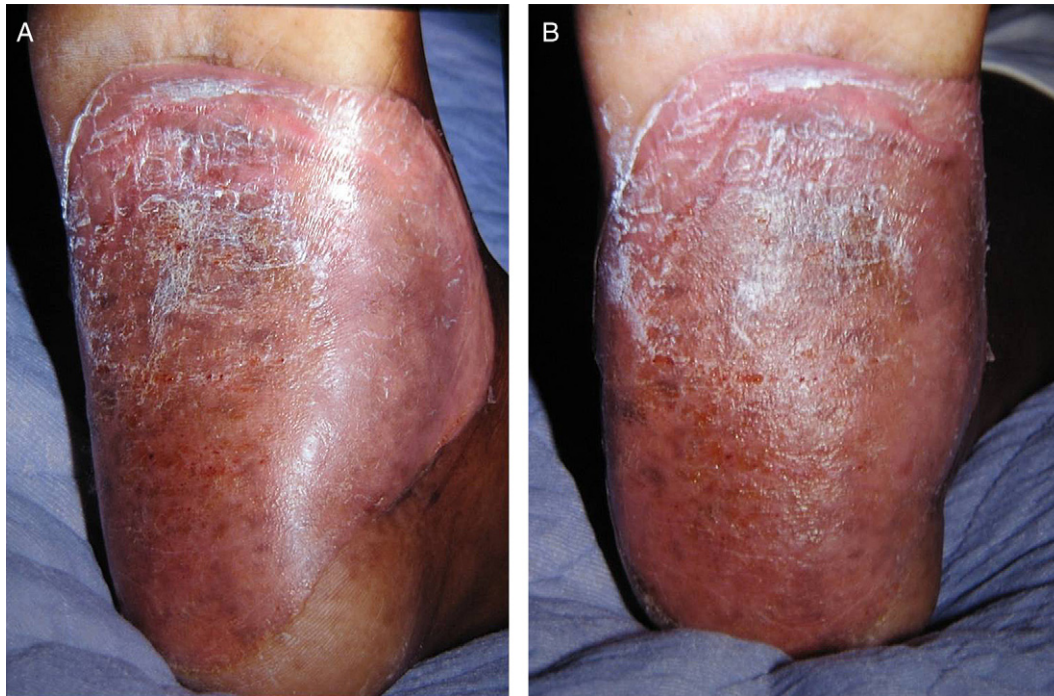
Fig. 7. (A) Clinical photograph showing the appearance of the lesion 1 week after intramuscular treatment with 2.4 million U of benzathine penicillin G. The active draining within the lesion ceased within the first 24 hours of treatment. (B) The roof of the lesion was then able to seal down to the underlying base, and the overlying skin became slightly thickened and dry, creating a more chronic-appearing skin condition as compared with the pretreatment findings.

dermal infiltration and proliferation of capillaries and lymphatics with endarteritis, as well as thrombosis and small areas of necrosis. Spirochetes, once identified with a silver stain, are now most commonly identified by means of direct fluorescent antibody staining (2).

Serologic studies include nontreponemal and treponemal tests for syphilis. Nontreponemal studies, such as the RPR, venereal disease research laboratory (VDRL) test, the unheated serum reagin, the automated reagin test, and the reagin screen test, detect antibodies to a cardiolipin-lecitin antigen, which comprises a small proportion of the lipid components found on the membranes of *Treponema pallidum*. The specificity of nontreponemal tests is low, and they are used primarily for screening and to follow disease activity. They will usually become positive 5 to 6 weeks after inoculation; however, about 25% of cases may be nonreactive. In some cases, moreover, the chancre may be completely resolved before the RPR or VDRL becomes positive. Nontreponemal tests are almost always positive in secondary syphilis, and a nonreactive test almost always excludes the diagnosis. The highest titers will be seen in secondary and latent stages of syphilis. Without treatment, titers will decline spontaneously toward the end of the latent stage and the VDRL will become negative in 25% of untreated patients (4). In a review of 54 cases of secondary syphilis, Puavilai et al (13) found that the duration of skin lesions and the VDRL titer were significantly correlated, but that skin lesion type and VDRL titer were not.

It is important to know conditions that are likely to produce false-positive results on nontreponemal tests. A patient who has been successfully treated for syphilis in the past may have a positive residual treponemal assay. Other situations or conditions that may cause a low titer false-positive result include technical error, inefficient absorbents, lyme borreliosis, genital herpes simplex, pregnancy, lupus erythematosus, recent immunization, alcoholic cirrhosis, scleroderma or mixed connective tissue disease (3, 4). When the clinical features appear atypical, careful correlation of patient history, laboratory data, and clinical features is necessary to exclude the possibility of another coincidental cutaneous eruption in the presence of a pre-existing positive VDRL (15).

Treponemal tests detect specific antibody to *Treponema pallidum* antigen and are more sensitive than nontreponemal tests. Assays include FTA-ABS, microhemagglutination assay for *T. pallidum*, hemagglutination treponemal test for syphilis, and treponemal immobilization. Treponemal tests usually remain positive for life and are therefore unhelpful in determining treatment success. However, if treated during primary syphilis, up to 25% of patients will revert to nonreactive status on treponemal tests (16). False-positive tests rarely occur, but have been reported with systemic and drug-induced lupus, mononucleosis, and leprosy (3). Most recently a case of congenital syphilis was reported to have occurred in a neonate. The great mimicker in that case presented as erythema multiforme–like targetoid skin lesions in a 1-day-old male newborn with early congenital syphilis (17).

In summary, the wide variety of presentations of secondary syphilis has earned it the epithet "the great mimicker." Although vesicular, bullous, or pruritic rashes argue against the diagnosis of syphilis and point toward more common conditions such as tinea infection, cases such as the one presented in this report illustrate the variability of syphilitic lesions and the need to maintain a high index of clinical suspicion. Any atypical rash should prompt further investigation, with syphilis on the list of differential diagnoses.

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