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The Great Mimicker: Forgotten but not Gone

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ABSTRACT

Once subdued after the advent of penicillin, syphilis has re-emerged in recent years, with incidence rates rising in many countries, including the United States. Its reputation as "the great imitator" is well earned due to its widely variable presentation, particularly in its second stage. This contributes to a high rate of delayed diagnosis and misdiagnosis, adding significant burden to patients and the health care system generally. Herein, we present 2 cases in which syphilis was misdiagnosed, leading to unnecessary therapies and delay of symptom clearance until treponemal tests were performed. In the context of recent epidemiologic trends and its notorious difficulty to clinically define, syphilis should always be considered in the differential diagnosis of diffuse cutaneous eruptions.

Introduction

Despite the availability of cheap, effective penicillin therapy, syphilis has resurged in many countries, including the United States, and remains a serious global public health problem. Syphilis progresses through 3 stages: primary, secondary, and tertiary. The presentation of secondary syphilis varies and often imitates other diseases, complicating diagnosis, and delaying curative treatment. We present 2 cases of secondary syphilis where diagnosis and management were delayed, emphasizing the importance of including secondary syphilis early in the differential diagnosis of diffuse cutaneous eruptions for prompt diagnosis and treatment. All patients provided informed consent.

Case 1

A 59-year-old male presented with a rash to his posterior neck, chest, abdomen, and back for over 6 months. The rash had been evaluated by multiple primary care physicians (PCPs), emergency medicine physicians, allergists, and oncologists, and treated with systemic and topical steroids. No antibiotics were prescribed. He denied any history of genital lesions, palmar or plantar rash, or oral lesions. Neither his wife nor anyone he had encountered had a rash or symptoms. He works in a shipyard and travels to various ports frequently.

Physical examination revealed erythematous, macular lesions without scale on the trunk, thighs, and posterior neck (Figure 1). No lesions were present on his face, head, palms, soles, genitals, or mouth. Because of the persistence of the diffuse rash for over 6 months despite treatment with steroids, a shave biopsy was taken from the left lateral superior chest to rule out atopic dermatitis versus cutaneous T-cell lymphoma (CTCL). Pathology revealed perivascular plasmacytic inflammation and endothelial swelling with spirochetes on *Treponema pallidum* immunohistochemical stain, consistent with secondary syphilis (Figure 2). A complete blood count (CBC), metabolic panel, human immunodeficiency virus (HIV), and rapid plasma regain (RPR) were conducted: RPR was positive, and he was treated with intramuscular (IM) penicillin G. Four weeks later, his rash had resolved.

Case 2

A 53-year-old female without significant medical history was referred to the cutaneous lymphoma clinic for a rash previously diagnosed as marginal zone lymphoma by a dermatopathologist following referral to a dermatologist by her PCP who had treated her unsuccessfully with oral and topical steroids for suspected psoriasis. The rash began 3-4 months prior on her trunk and spread to her extremities. Additional history included unintentional weight loss but was negative for other constitutional symptoms.

Physical examination revealed numerous erythematous, faintly scaly plaques and nodules across the trunk, neck, and flexor aspects of the upper and lower extremities (Figure 3), with a notable pink patch on the

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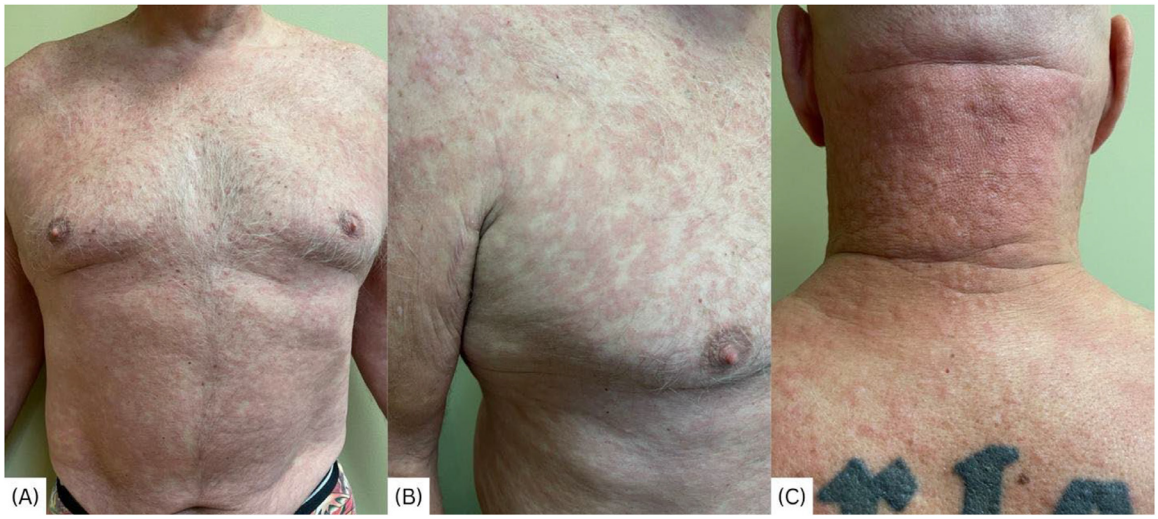

Figure 1. Erythematous macular lesions without scale.

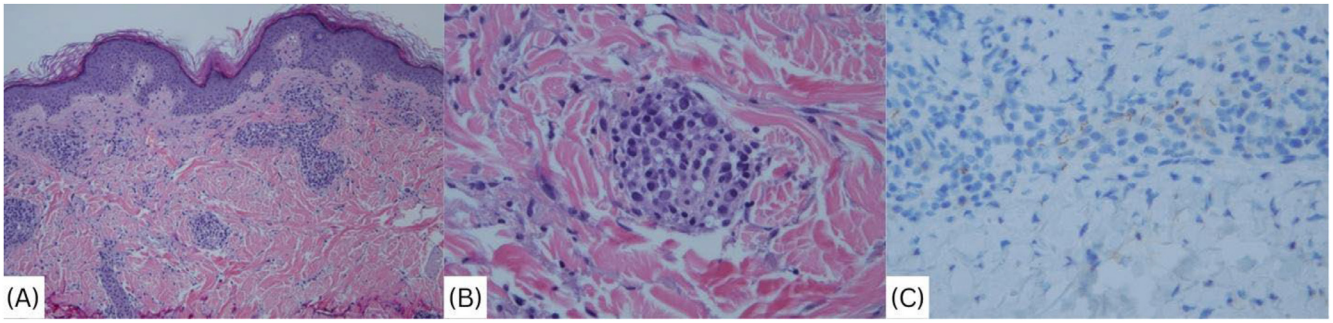

Figure 2. **(A)** Perivascular plasmacytic infiltrate and endothelial swelling (H&E stain, ×100). **(B)** Plasma cells (H&E stain, ×400). **(C)** Spirochetes seen on *Treponema pallidum* immunohistochemical stain (×400).

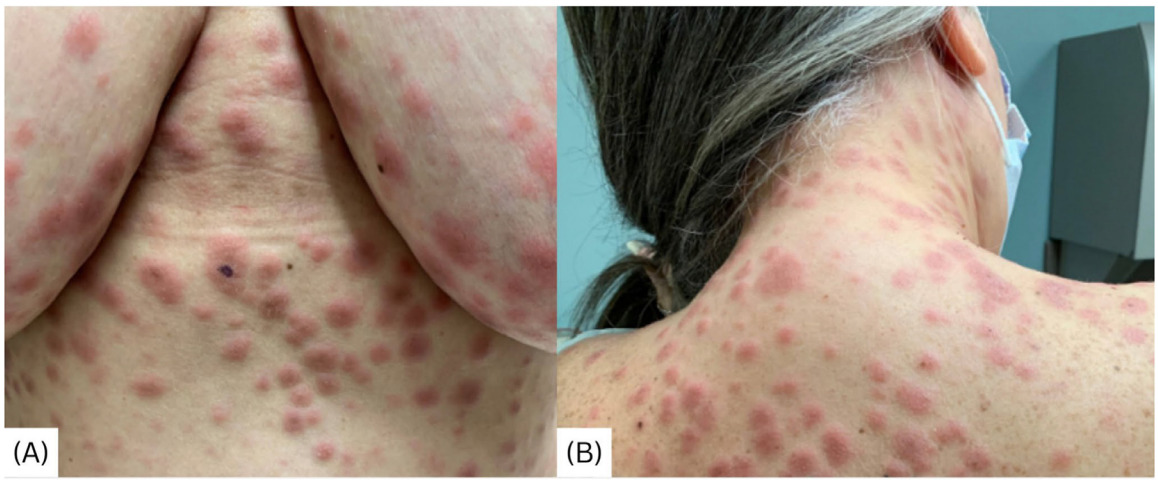

Figure 3. Numerous erythematous faintly scaly plaques and nodules.

left palm. A repeat punch biopsy was taken from her abdomen. Flow cytometry, blood counts, lactate dehydrogenase (LDH), HIV, and human T-lymphotropic virus (HTLV) tests were unremarkable. Screening RPR and confirmatory *Treponema pallidum* particle agglutination (TPPA) were reactive. Positron emission tomography/computed tomography (PET/CT) showed extensive cutaneous lesions associated with fluorodeoxyglucose (FDG) avid multi-compartmental adenopathy on both sides of the diaphragm with increased activity in the tonsillar regions bilaterally.

A second biopsy and review of the original biopsy both revealed a dermal infiltrate with perivascular and periadnexal distribution patterns largely composed of lymphocytes, histiocytes, and numerous plasma cells (Figure 4A). Although there was a predominance of κ-positive plasma cells by in situ hybridization, no definitive monotypic plasma cells were noted via κ and λ immunohistochemistry. A spirochete study showed numerous treponemal spirochetes in the epidermis and dermis (Figure 4B).

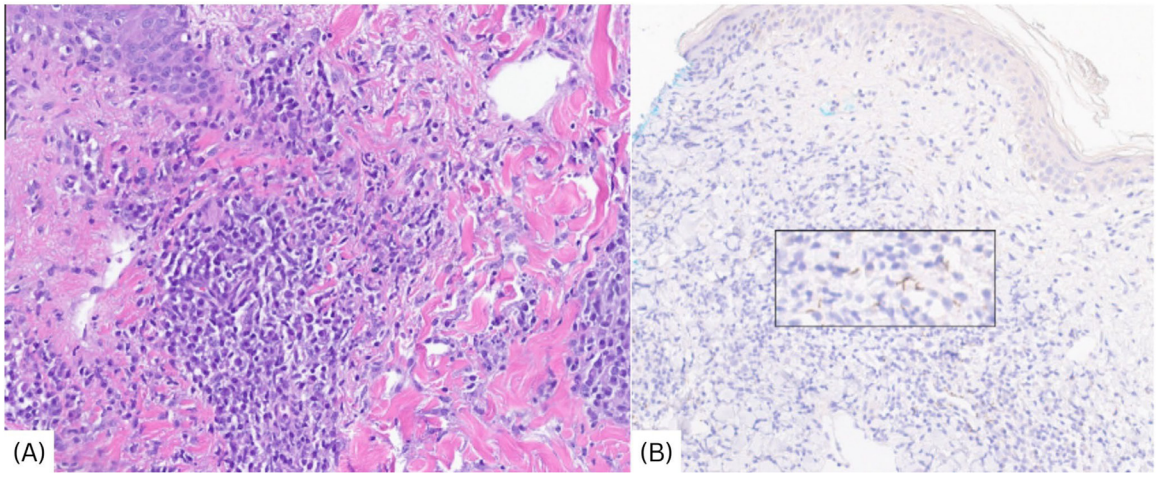

Figure 4. **(A)** Perivascular and periadnexal infiltrate largely composed of lymphocytes, histiocytes, and numerous plasma cells (hematoxylin and eosin staining). **(B)** Spirochete study shows numerous coiled treponemal spirochetes in the epidermis and dermis.

A diagnosis of secondary syphilis was made, and the patient was treated with Penicillin G. At the 2-week follow-up, the patient's rash and symptoms had resolved.

Discussion

Syphilis cases in the United States have surged to the highest rates in more than 70 years, according to the Centers for Disease Control and Prevention.[1] From 2020 to 2021, syphilis cases increased by 31.7% (from 40.4 to 53.2 per 100,000), the highest total number of cases since 1950.[1] Rates increased in all regions of the United States, among males and females, in all racial/ethnicity groups, and all age groups.[1]

Untreated primary syphilis may progress to secondary syphilis about 6-8 weeks after the primary infection. Symptoms may include fever, malaise, myalgia, sore throat, and most commonly a rash.[2] The classic cutaneous presentation is a painless, nonpruritic macular rash with reddish- or copper-colored lesions on the palms of the hands or soles of the feet.[2,3] However, the rash can be extremely variable and may present as macular, papular, maculopapular, papulosquamous, lichenoid, nodular, or pustular lesions. Cutaneous manifestations often imitate psoriasis, contact dermatitis, atopic dermatitis, pityriasis rosea, drug eruptions, lymphoproliferative diseases, etc.[4,5]

Our cases illustrate syphilis often being mistaken for other conditions. The first patient had a rash for over 6 months despite receiving treatment with topical and systemic steroids from multiple outside physicians. In fact, the cutaneous manifestations of secondary syphilis usually self-resolve (ie, latency) by 6 weeks. It is probable that the systemic steroids prolonged the duration of the macules. In the context of syphilis, the use of steroids may mask the symptoms and delay proper diagnosis and treatment. The second patient was originally misdiagnosed with guttate psoriasis and then marginal zone lymphoma before syphilis was identified. Both cases were solved once treponemal tests were performed. These long and complicated courses can contribute to significant distress for patients as well as to unnecessary costs and transmission.

The frequency of misdiagnosis of secondary syphilis can vary and is challenging to exactly quantify. The rate of misdiagnosis depends on factors, such as the clinician's experience and the patient's specific symptoms. Increased awareness and thorough evaluation can reduce misdiagnosis. Amid continued rising syphilis infections, clinicians should maintain a high suspicion for treponemal infections in diffuse cutaneous eruptions and test early, even with atypical dermatological presentations.

Conclusion

Given that the cutaneous presentation of syphilis can share clinical and histological features of numerous other conditions and the evolving epidemiologic landscape, clinicians should include syphilis on the differential for diffuse eruptions and order appropriate testing (eg, serology and stains), so prompt therapy can be administered. Prompt diagnosis and treatment of syphilis in patients and their sexual contacts is crucial in mitigating the disease's resurgence.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

CRediT authorship contribution statement

Blayne E. Fenner: Conceptualization, Data curation, Formal analysis, Resources, Writing – original draft, Writing – review & editing. **Kevin M. Burningham:** Conceptualization, Writing – original draft, Writing – review & editing. **Jamael L. Thomas:** Conceptualization, Writing – original draft, Writing – review & editing. **Brent C. Kelly:** Conceptualization, Formal analysis, Writing – review & editing. **Auris O. Huen:** Conceptualization, Formal analysis, Writing – review & editing. **Stephen K. Tyring:** Conceptualization, Data curation, Formal analysis, Writing – review & editing.

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