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Authors

Wang, Apphia
Risner-Rumohr, Sara
Rodriguez-Waitkus, Paul
et al.

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Case Presentation

Secondary syphilis: a case mimicking erythema multiforme clinically and pathologically

Apphia Wang, Sara Risner-Rumohr MD, Paul Rodriguez-Waitkus MD PhD, Harry Dao MD

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Department of Dermatology, Baylor College of Medicine, Houston, Texas.

Department of Pathology & Immunology, Baylor College of Medicine, Houston, Texas.

Correspondence:

Apphia Wang
Baylor College of Medicine
Houston, TX

Abstract

Secondary syphilis, the hematogenous spread of *Treponema pallidum*, usually occurs 4-10 weeks after initial exposure. The skin is involved in 70% of cases, with maculopapular, vesiculobullous, and ulcerative morphologies possible at presentation, making the diagnosis of secondary syphilis challenging given its ability to mimic many other conditions. We present an atypical case of secondary syphilis that closely resembled erythema multiforme (EM) clinically and histologically.

Introduction

Secondary syphilis, the hematogenous spread of *Treponema pallidum* usually acquired via sexual contact generally occurs within 4-10 weeks after initial exposure [1]. The skin is involved in 70% of cases ranging from maculopapular lesions to ulcers, making the diagnosis of secondary syphilis challenging given its ability to mimic many other dermatologic conditions [2]. Genital and extragenital involvement including condyloma lata, oral mucous patches, scalp alopecia, and lues maligna have all been described as forms of secondary syphilis; bone, and meningeal involvement may also be present [1,3]. We present an atypical case of secondary syphilis that mimicked erythema multiforme both clinically and histologically.

Case report

A 29-year-old woman presented with a one month history of symmetric discrete targetoid hyperpigmented papules and patches, some coalescing into plaques, involving the palms, soles, and dorsal hands and feet. These eruptions persisted despite prior treatment with oral prednisone and spread to involve the trunk and extremities; no genital lesions were visualized. She noted an associated burning sensation. Her last unprotected sexual encounter was reportedly over a year prior to presentation.

A punch biopsy was taken from the right wrist and acyclovir was started given the clinical suspicion of recurrent EM related to underlying HSV reactivation. Histologically, the wrist biopsy showed acral skin with an interface dermatitis composed of lymphocytes and histiocytes associated with hydropic changes and rare dyskeratosis. The dermis contained a mild superficial perivascular infiltrate composed predominantly of lymphocytes. No psoriasiform epidermal hyperplasia or plasma cells were identified. The histological features of this biopsy mimicked erythema multiforme. A spirochete immunohistochemical stain, with appropriate control, showed multiple intraepidermal spirochetal microorganisms, compatible with *Treponema pallidum*. Lab results showed negative HIV and positive RPR. Therapy with penicillin G was initiated, followed by full recovery and resolution of the cutaneous eruption.

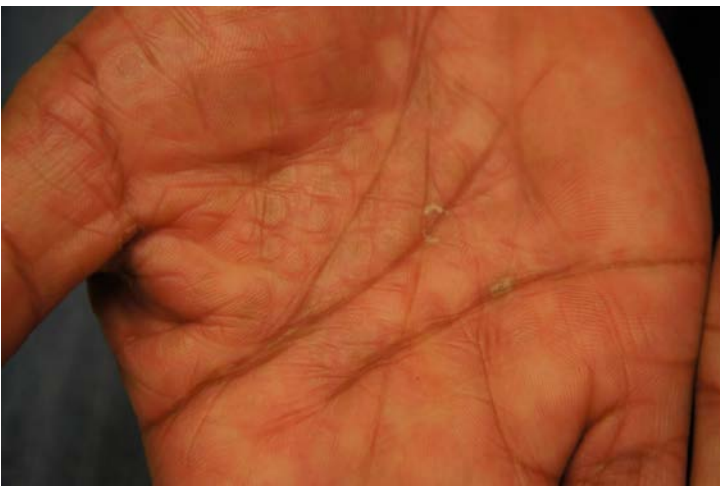


Figure 1. Multiple palmar targetoid macules with desquamation



Figure 2. Multiple bilateral plantar targetoid macules with desquamation



Figure 3. Multiple hyperpigmented targetoid macules with desquamation on dorsal foot

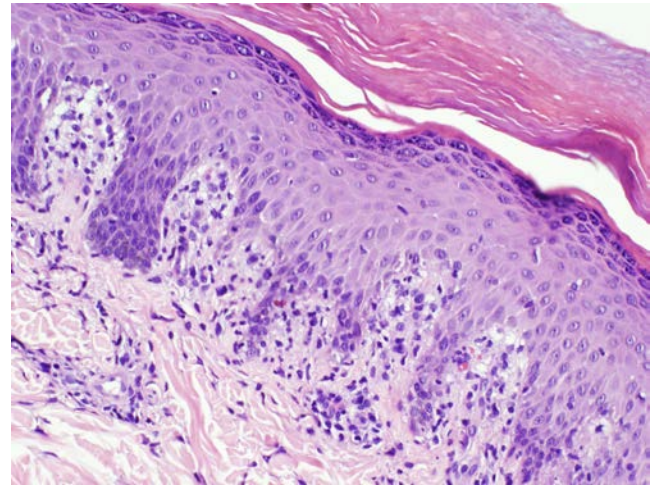


Figure 4. H&E sections show acral skin with an interface infiltrate composed of lymphocytes and histiocytes associated with hydropic changes and rare dyskeratosis (40x)

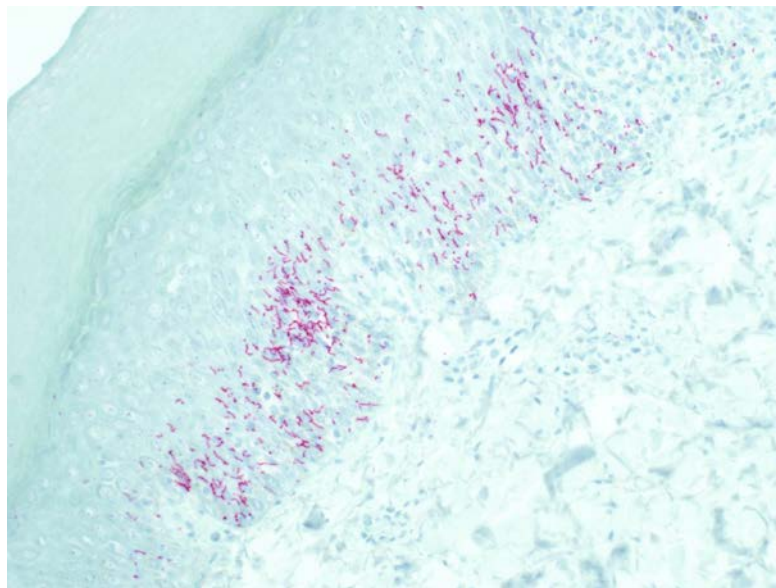


Figure 5. Immunohistochemical staining reveals multiple intraepidermal spirochetal microorganisms (red stain) compatible with *Treponema pallidum* (40 x)

Discussion

Secondary syphilis is one of the three stages of syphilis caused by *Treponema pallidum*. This stage generally occurs 4-10 weeks after sexual contact and presents with mucocutaneous lesions, lymphadenopathy, and systemic symptoms including flu-like symptoms and hepatosplenomegaly [4]. The syphilitic hallmark findings of endothelial cell proliferation and perivascular dermal infiltrate of plasma cells were not observed, although they are not required to establish the diagnosis [5]. The interface dermatitis with other features suggestive of erythema multiforme present in our case is consistent with histologic findings in other cases reported.

EM is considered a self-limited hypersensitive response to foreign antigen including infectious agents and medications [5]. Typical histological findings include prominent vacuolization of the basal cells with multiple necrotic keratinocytes [6]. Rare cases of secondary syphilis-induced EM have been described in the literature using PCR showing specific bands of *T. pallidum* DNA products, along with confirmatory immunohistochemical stains using tissue from the clinically and histologically EM-like lesions [5,6,10]. It has been hypothesized that these syphilis-induced EM lesions arise from a specific immune response against antigens of *T. pallidum* via formation of immune complexes [10].

The skin is involved in 70% of secondary syphilis cases and syphilis has been named the “great mimicker” given its polymorphic appearance. It is estimated that approximately 40–85% of women and 20–65% of men do not experience the classic chancre of primary syphilis [7]. Therefore, it is essential to include syphilis in the differential diagnosis, especially in patients with extragenital lesions.

The differential diagnosis for cases of bilateral hand and foot eruptions include syphilis, erythema multiforme, hand-foot-mouth disease, and Rocky Mountain spotted fever. The diagnosis of syphilis can be confirmed in fresh smears from a chancre by finding spirochetes on dark field microscopy. The disease can be confirmed in tissue by use of the Warthin-Starry stain, immunohistochemical analysis, or by PCR. Serological diagnosis can also be obtained with VDRL (venereal disease research laboratory), RPR (rapid plasma regain), FTA-ABS (fluorescent treponemal antibody absorption test), and microhemagglutination assay (MHA-TP). In HIV positive patients, however, it has been suggested that pathological staining or PCR be used to help make the diagnosis of EM-like syphilis, instead of relying solely on serologic tests [9].

To our knowledge, there are only six cases of EM-like secondary syphilis published in the literature (Table 1). Even though rare in occurrence, syphilis should be considered in the differential diagnosis in cases with clinical and pathological findings consistent with EM.

Table 1. Clinical, Pathological, and Serological Features of EM-like Secondary Syphilis in the Literature

Case no.	Age/sex	Site of	Clinical history	Pathological features	HIV status	HSV status	Syphilis serologies	Syphilis stains	PCR
1	20 M	Oral mucosa, trunk, extremities	4 day history of pruritic targetoid eruptions	Vacuolar interface dermatitis with necrotic keratinocytes	+ western blot; CD4 209/mL; bisexual	+ HSV 1 & 2 IgG; - HSV 1 & 2 IgM	VDRL 1:256; TPHA 1:5120 → 2 months later VDRL 1:128	+ IHC for spirochetes	<i>T. pallidum</i> <i>polA</i> 377-bp product
2	37 F	Palms	6 week history of pruritic targetoid lesions	Interface dermatitis, hyperkeratosis, lymphocytic exocytosis, basal layer vacuolization			VDRL 1:32; +TPHA; + FTA-ABS-IgM	- Warthin-starry	<i>T. pallidum</i> 658bp product
3	23 F	Lower face, trunk, groin, extremities	2 month history of pruritic plaques, alopecia, mucosal erosion	Swollen endothelial cells with superficial perivascular infiltrate with plasma cells	- HIV rapid test; - HIV RNA PCR		RPR 1:32 (1:64 on repeated test); + FTA-ABS	- Warthin-starry	- <i>T. pallidum</i> PCR
4	26 M	Head, neck, trunk, extremities	5 day history of pruritic rashes and fever	Hyperkeratosis, parakeratosis, lymphocytic exocytosis, epidermal apoptotic keratinocytes, vacuolar degeneration of basal cell layer, superficial perivascular lymphohistiocytic infiltration	+ HIV ELISA; + western blot; CD4 482/mm ³ ; HIV viral load 288,000 copies/mL; homosexual	- HSV	VDRL 1:128 ; TPHA 1:2560	+ IHC for spirochetes	
5	1-day-old M	Face, back, buttocks, extremities	1 day history of bullous, targetoid lesion, respiratory distress, hepatosplenomegaly, anemia, cyanosis,	Scattered dyskeratotic cells in epidermis and interface dermatitis		- Tzanck smear	VDRL 1:256; CSF VDRL 1:32 → VDRL 1:4 after 3 months → 1:1 after 1 year	- Warthin-starry	<i>T. pallidum</i> DNA <i>pol I</i> 174 bp product
6	37 F	Forearms,	5 month history of	Interface dermatitis,			VDRL 1:64 ;	+ IHC	

palms,
soles

pruritic lesions,
genital and oral
ulcers

hyperkeratosis,
lymphocytic exocytosis,
vacuolization of basal layer,
dermal perivascular
lymphohistiocytic infiltrate
without plasma cells

+TPHA; + FTA-
ABS → after 7
months VDRL 1:2

for
spiroche
tes

Plasma Reagin
VDRL, Venereal Disease Research Laboratory
TPHA, Treponema Pallidum Hemagglutination Assay
FTA-ABS, Fluorescent Treponemal Antibody-Absorption
IHC, Immunohistochemistry

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