A Peculiar Pattern: Nodular Secondary Syphilis with Granulomatous Dermatitis

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ABSTRACT

Nodular syphilis with a granulomatous inflammatory histopathologic pattern is an uncommon cutaneous presentation of secondary syphilis which could pose a diagnostic challenge for clinicians and pathologists alike.

A 33-year-old male diagnosed with HIV presented with a 5-week history of asymptomatic generalized erythematous papules and nodules with overlying scales, with involvement of the palms and soles. Histopathologic examination of a nodule from the forearm revealed non-caseating granulomas in a background of a mixed cell inflammatory infiltrate composed of lymphocytes, epithelioid and foamy histiocytes, plasma cells, neutrophils, and multinucleated giant cells. Warthin-Starry Stain revealed spirochetal organisms, while Fite-Faraco and Periodic Acid-Schiff stains were negative for acid-fast bacilli and fungal elements, respectively. Rapid plasma reagin (RPR) was reactive (1:256). Patient was given a single dose of benzathine penicillin G 2.4 million units intramuscularly, with noted complete resolution of skin lesions as well as an 8-fold decrease in RPR titers.

Nodular lesions are an uncommon cutaneous manifestation of secondary syphilis, and the associated histopathologic finding of granulomatous inflammatory pattern is also unusual, posing a diagnostic challenge. With the increasing prevalence of syphilis, especially among HIV patients, dermatologists, dermatopathologists, internists, and infectious disease specialists should be aware of such presentations of syphilis.

Keywords: syphilis, nodular, granulomatous, atypical

INTRODUCTION

Syphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum*.[1] Its incidence continues to rise, especially in men who have sex with men (MSM), and those who have multiple sexual partners. It leads to significant complications if left untreated and is a frequent co-infection of human immunodeficiency virus (HIV) as syphilis facilitates the transmission of the virus.[2]

Syphilis presents in three stages: primary, secondary, and tertiary syphilis. Primary syphilis presents with a painless ulcer at the site of inoculation, which often goes unnoticed by the patient. Secondary syphilis has a wider clinical presentation, with both cutaneous and systemic symptoms. The most common cutaneous lesions of secondary syphilis are erythematous macules or maculopapules distributed symmetrically on the trunk and extremities. However, skin lesions could be quite varied, leading to challenges in clinical diagnosis. Untreated primary or secondary syphilis may eventually progress into tertiary syphilis, with more significant morbidity including cardiovascular and neurologic complications, as well as debilitating deformities caused by gummatous infiltration of organs.[1,3] Here we report an unusual presentation of secondary syphilis in a 33-year-old male HIV patient.

eISSN 2094-9278 (Online)
Published: September 30, 2024
https://doi.org/10.47895/amp.v58i17.9040

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CASE DESCRIPTION

A 33-year-old Filipino male presented with a 5-week history of generalized erythematous papules and nodules, some with overlying collarette scaling, starting on the arms, spreading to the trunk and lower extremities, with fewer lesions on the face and the palmoplantar skin (Figure 1). These were not associated with any pain or pruritus, but manipulation of lesions would lead to erosions. There were no associated systemic symptoms, nor any oral or anogenital lesions noted at the time. He was diagnosed to be infected with HIV a month prior through serology, with an initial CD4 count of 259 cells/mm^3. He was immediately started on tenofovir and lamivudine. He has no other co-morbidities such as hypertension, diabetes, heart disease, or cancer. The patient, however, was diagnosed with anogenital warts in the past, for which electrodessication with curettage was done. He denies prior history of other sexually transmitted diseases such as syphilis, gonorrhea, or herpes. Upon review of sexual history, the patient practices anal receptive sex, and has had four male sexual partners with only occasional condom use. His last sexual contact was around seven months prior to the onset of the skin lesions. He does not recall any similar symptoms in his previous partners. The primary consideration at the time was secondary syphilis due to the scaly papulonodules with palmoplantar involvement with the background of the diagnosis of HIV, as well as due to the temporality from the last sexual contact from which he could have acquired the infection. A rapid plasma reagin (RPR) test was ordered, and a 4-mm punch biopsy was performed on a nodule on the left arm. RPR test revealed a reactive (1:256) result and was then treated with a single dose of benzathine penicillin G 2.4 million units intramuscularly, following the Centers for Disease Control and Prevention (CDC) guidelines for the treatment of secondary syphilis in persons with HIV infection. However, the biopsy results revealed non-caseating granulomas in a background of a mixed cell inflammatory infiltrate composed of lymphocytes, epithelioid and foamy histiocytes, plasma cells, neutrophils, and multinucleated giant cells (Figure 2). These findings led to other differentials such as a mycobacterial or a deep fungal infection, and thus stains were requested to further help in the diagnosis. Warthin-Starry Stain revealed spirochetal organisms (Figure 3) within the granulomas in the dermis, while Fite-Faraco and Periodic Acid-Schiff (PAS) stains were negative for acid-fast bacilli and fungal elements, respectively. Other laboratory tests such as cultures were also recommended. However, on follow-up of the patient one month after the penicillin treatment, there was already complete resolution of the skin lesions further supporting the diagnosis of secondary syphilis. Repeat RPR after three months revealed an 8-fold decrease in titers (1:32).

DISCUSSION

Due to its protean and sometimes subtle clinical presentation, syphilis, particularly in its secondary stage, has been called the "great mimicker."[3,4] The cutaneous manifestations of secondary syphilis, classically termed "syphilids", often present as a generalized and symmetric eruption. This eruption commonly presents as red-brown ("copper-colored"), scaly macules and papules on the trunk and extremities, including the palms and soles.[5] Other forms of presentation include follicular, lichenoid, vesicular, psoriasiform, corymbiform, hypertrophic papules, and also pustular, annular and rarely, nodular lesions.[4] The papulonodular presentation with granulomatous

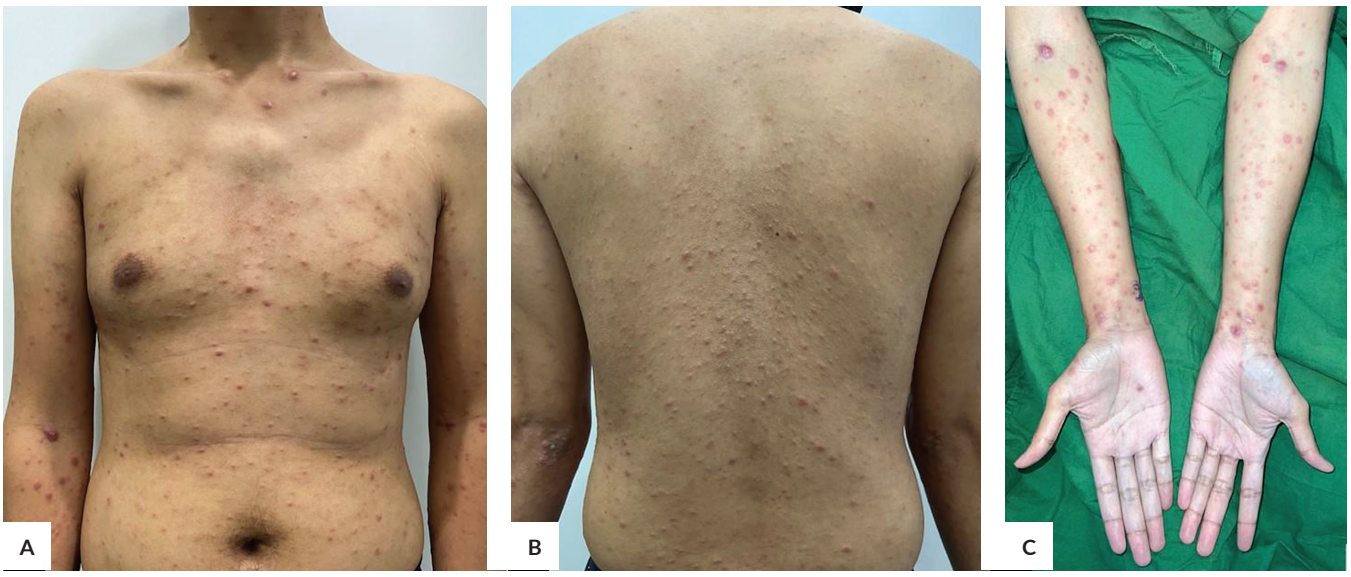

Figure 1. (A, B, and C) Multiple erythematous to violaceous papules and nodules, some with overlying scales on the trunk and extremities, with few erythematous papules on the palms.

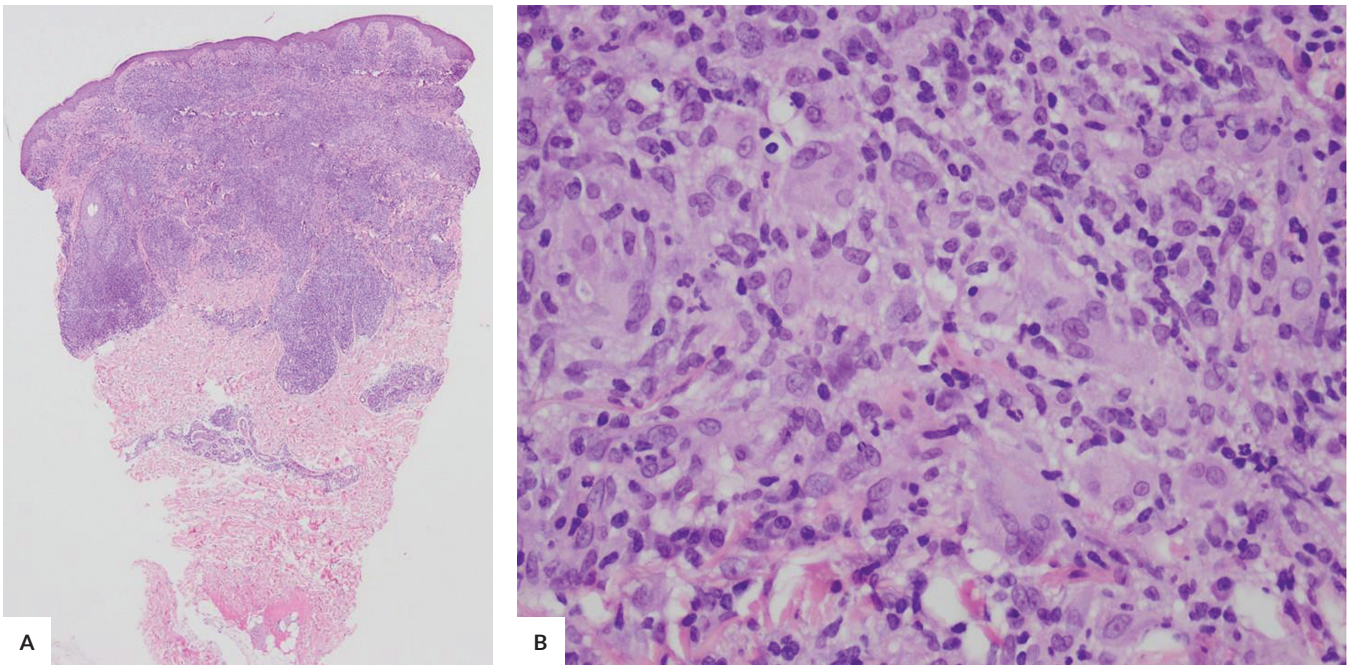

Figure 2. **(A)** Dense diffuse inflammatory infiltrates in the superficial to mid dermis; **(B)** Inflammatory infiltrates are composed of lymphocytes, epithelioid and foamy histiocytes, plasma cells, neutrophils, and multinucleated giant cells (40x).

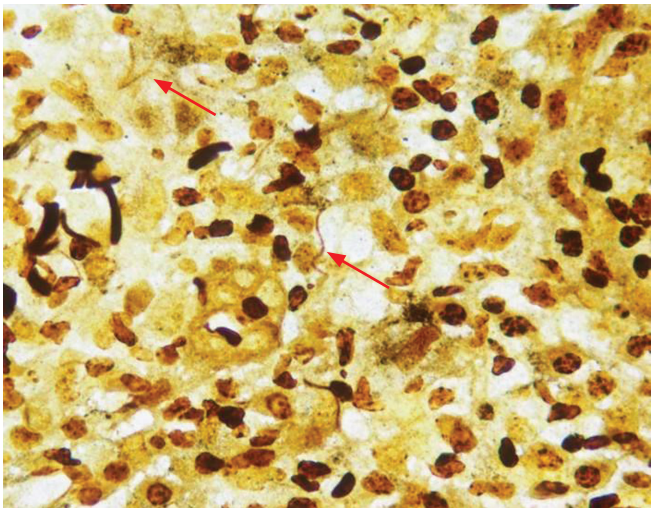

Figure 3. Warthin-Starry stain showing spirochetal organisms *(red arrows)* within the granulomas in the dermis.

inflammation has been described more commonly in tertiary syphilis, but cases of granulomatous secondary syphilis have been reported.[6] Most of these secondary syphilis cases have sparing of the palms and soles, and a review by Rysgaard et al. of granulomatous secondary syphilis cases showed a significant correlation between the presence of nodules and absence of palmoplantar lesions.[7] In the case of our patient, most of the nodules are on the trunk and extremities, with only a few papules on the palms and soles. In most cases of atypical presentation of secondary syphilis, other clues that could help in the diagnosis are the presence of mucosal ulcerations, involvement of palmoplantar skin, as well as genital lesions. In the absence of these, reaching a clinical diagnosis of secondary syphilis may be difficult.[4]

The most frequent histopathologic pattern in secondary syphilis is psoriasiform hyperplasia, frequently with spongiosis and vacuolar alterations.[8] In a review by Liu and Li of 59 specimens from secondary syphilis patients, the most common histologic findings included plasma cells, irregular acanthosis, elongated rete ridges, and endothelial swelling.[9] Granulomatous inflammation is not a common histopathologic pattern found in secondary syphilis. It has been hypothesized that nodular granulomatous skin lesions more frequently occur with longer disease duration (late stage of secondary syphilis), and that they could occur as a hypersensitivity reaction to the treponemal organisms.[10] In individuals with depressed immunity, the occurrence of syphilis may produce modified reactions to the disease. Massive numbers of *Treponema pallidum* may be found, and formation of granulomas may be a resultant reaction to this.[11] This uncommon finding may represent a diagnostic pitfall in the histopathologic examination of specimens from suspected syphilis cases.[12] Furthermore, classically used silver stains such as Warthin–Starry and Levaditi stains to highlight spirochetes may often lead to false positive or false negative results due to difficulties in differentiating from staining of background tissue elements.[10] Immunohistochemical stain for *Treponema pallidum* antibody is now regarded to be more sensitive and specific in the tissue diagnosis of syphilis but is currently unavailable at our institution.[13]

In our patient's case, due to the granulomatous pattern seen on biopsy, other differentials were considered such as a mycobacterial or a deep fungal infection. Invasive mycoses among HIV patients like cryptococcosis, histoplasmosis, and penicilliosis may present with widespread papulonodules similar to our patient's, but due to the lack of other systemic symptoms, these were not highly considered. Non-infectious histopathologic differentials for granulomatous dermatitis are broad and include granuloma annulare, sarcoidosis, xanthogranuloma, and granulomatous drug reactions. However, these entities would present differently, and thus were not highly considered as well. Specific histopathologic features of these conditions were also not found in the biopsy of our patient, such as palisading granulomas surrounding degenerated collagen for granuloma annulare, noncaseating epithelioid "naked" granulomas for sarcoidosis, Touton-type giant cells for xanthogranuloma, and eosinophilic infiltrates for drug reaction. Furthermore, the findings of spirochetal organisms on Warthin-Starry stain, the negative Fite-Faraco and PAS stains, and the complete resolution with penicillin treatment all supported the diagnosis of secondary syphilis for the patient.

The CDC recommends treatment of secondary syphilis with benzathine penicillin G 2.4 million units intramuscularly in a single dose.[14] There is no difference in management for nodular granulomatous secondary syphilis based on current literature, but this uncommon presentation should lead to a higher suspicion for other atypical presentations of syphilis in the patient, regardless of stage, which may warrant a more aggressive treatment.

CONCLUSION

Nodular skin lesions are an uncommon cutaneous manifestation of secondary syphilis, and the associated histopathologic finding of granulomatous inflammatory pattern is also unusual. In HIV patients presenting with widespread nodular skin lesions, it is important to consider secondary syphilis in the differentials aside from other infections for which HIV is a risk factor, such as mycobacterial infections or invasive mycoses. This atypical presentation of syphilis may bring about difficulties in the diagnosis and possible delays in treatment. With the increasing prevalence of syphilis, especially among HIV patients, dermatologists, dermatopathologists, internists, and infectious disease specialists should be aware of such presentations of syphilis.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This paper was funded by the authors. No external funding agency.

REFERENCES

1. Tudor ME, Al Aboud AM, Leslie SW, Gossman W. Syphilis. In: StatPearls [Internet]. Updated 2023 May 30 [cited 2023 Nov 4]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK534780/
2. Kojima N, Klausner JD. An update on the global epidemiology of syphilis. Curr Epidemiol Rep. 2018 Mar;5(1):24-38. doi: 10.1007/s40471-018-0138-z. PMID: 30116697; PMCID: PMC6089383.
3. Peeling RW, Mabey D, Kamb ML, Chen XS, Radolf JD, Benzaken AS. Syphilis. Nat Rev Dis Primers. 2017 Oct 12;3:17073. doi: 10.1038/nrdp.2017.73. PMID: 29022569; PMCID: PMC5809176.
4. Lee GL, Gru AA, Wong HK, Nagarajan P. Granulomatous syphilis: a pattern to remember. Case Report and Review of Literature. Clin Microbiol Open Access. 2015;4(1):1-5. doi:10.4172/2327-5073.1000184.
5. Whiting C, Schwartzman G, Khachemoune A. Syphilis in dermatology: recognition and management. Am J Clin Dermatol. 2023 Mar;24(2):287-97. doi: 10.1007/s40257-022-00755-3. PMID: 36689103; PMCID: PMC9869822.
6. Raman A, Deo K, Sharma YK, Iqbal B, Mirza S, Gupta A. Nodular secondary syphilis with granulomatous inflammation. Indian J Sex Transm Dis AIDS. 2022 Jan-Jun;43(1):91-3. doi: 10.4103/ijstd.ijstd_91_21. PMID: 35846533; PMCID: PMC9282688.
7. Rysgaard C, Alexander E, Swick BL. Nodular secondary syphilis with associated granulomatous inflammation: case report and literature review. J Cutan Pathol. 2014 Apr;41(4):370-9. doi: 10.1111/cup.12293. PMID: 24447075.
8. Purnamasari I, Hidayati AN, Kusumastuti EH, Effendy I. The histopathological features of syphilis and its mimickers. Folia Medica Indonesiana. 2023;59(1):63–9. doi: 10.20473/fmi.v59i1.37286.
9. Liu XK, Li J. Histologic features of secondary syphilis. Dermatology. 2020;236(2):145-50. doi: 10.1159/000502641. PMID: 31536976.
10. Magdaleno-Tapial J, Valenzuela-Oñate C, Ortiz-Salvador JM, Hernández-Bel P, Alegre-De Miquel V. Treponema pallidum epidermotropism in nodular secondary syphilis. Indian J Dermatol. 2018 Nov- Dec;63(6):509-11. doi: 10.4103/ijd.IJD_232_18. PMID: 30504982; PMCID: PMC6233049.
11. Carlson JA, Dabiri G, Cribier B, Sell S. The immunopathobiology of syphilis: the manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. Am J Dermatopathol. 2011 Jul;33(5):433-60. doi: 10.1097/DAD.0b013e3181e8b587. PMID: 21694502; PMCID: PMC3690623.
12. Ambrogio F, Cazzato G, Foti C, Grandolfo M, Mennuni GB, Vena GA, et al. Granulomatous secondary syphilis: a case report with a brief overview of the diagnostic role of immunohistochemistry. Pathogens. 2023 Aug 18;12(8):1054. doi: 10.3390/pathogens12081054. PMID: 37624014; PMCID: PMC10457844.
13. Pettit C, McMurray S, Randall MB, Jones A, Fisher K. Highlighting a potential pitfall: positive Treponema pallidum immunohistochemical stain in a patient without syphilis. Am J Dermatopathol. 2019 Dec;41(12):924-6. doi: 10.1097/DAD.0000000000001443. PMID: 31389806.
14. Centers for Disease Control and Prevention - Sexually Transmitted Infections Treatment Guidelines, 2021-Syphilis Among Persons with HIV Infection [Internet]. [cited 2024 Jan 29]. Available from: https://www.cdc.gov/std/treatment-guidelines/syphilis- hiv.htm#print.