

## Granulomatous Syphilis: A Pattern to Remember. Case Report and Review of Literature

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### Abstract

Granulomatous inflammation in secondary syphilis is rare and poses diagnostic challenges both on clinical grounds and histologically. We report a case of granulomatous syphilis in a 44-year-old woman that presented with an erythematous papulo-nodular rash involving her face, neck and upper portions of chest, back and arms that was initially diagnosed as urticaria and treated ineffectively with systemic steroids. No mucosal or genital lesions, involvement of soles and palms, or lymphadenopathy was present. Histopathologic examination revealed dense dermal perivascular and periadnexal inflammatory infiltrate composed of lymphocytes and plasma cells accompanied by prominent granulomatous inflammation. Anti-treponemal immunohistochemical study revealed spirochetes and along with positive serology, supporting the diagnosis of secondary syphilis. With an increasing number of reported syphilis cases recently, internists, infectious disease specialists, dermatologists and dermatopathologists alike should be aware of the unusual presentations of this great imitator. We also present a review of literature of cases of secondary syphilis that present in such unusual clinical and histologic phenotypes.

**Keywords:** Granulomatous; Syphilis; Atypical

### Introduction

The incidence of syphilis, a sexually transmitted disease caused by *Treponema pallidum* subsp. *pallidum* is on the rise in the United States [1]. After an all-time low of 2.1 cases of primary and secondary syphilis per 100,000 population in 2000 [2], there has been a steady increase in the number of reported cases of syphilis [3]. In 2013, 16,663 cases of primary and secondary syphilis were reported, with a rate of 5.3 cases per 100,000. While more than 90% of the syphilis cases are reported in men, the number of women affected by the disease has been slowly decreasing.

The incidence of primary syphilis is very likely to be under-reported since most patients are frequently asymptomatic and are unaware of the presence of the asymptomatic chancre, particularly in the absence of secondary infections. About a fourth of the untreated patients with primary syphilis fail to clear the infection and proceed to the secondary stage [4,5]. The clinical manifestations of secondary syphilis consist of non-specific symptoms (fever, headache, malaise and weight loss), but also typical findings including maculo-papular skin rash, lymphadenopathy, condyloma lata, and mucosal ulcers [6]. Systemic manifestations such as uveitis, retinitis, alopecia, arthritis, osteitis, meningitis, cranial neuropathies, glomerulonephritis, and hepatitis may also be seen. Though the most common skin rash is the maculopapular eruption, in some patients, the cutaneous involvement can be quite varied, leading to difficulties with clinical recognition [7,8]. Here, we report a case of atypical secondary syphilis in a 44-year-old woman that was initially diagnosed as urticaria.

### Case Report

A 44-year-old Caucasian woman presented with a 4-week history of generalized painful rash, malaise, and myalgia. The rash initially began on her face as asymptomatic, small, pink lesions which then spread caudally to her neck, chest, upper back, and proximal extremities. She had initially been diagnosed with acute urticaria and was treated with systemic steroids at an outside facility. However, the rash persisted, continued to progress and eventually also became tender. Physical

examination revealed multiple edematous and indurated pink papules, which in some areas coalesced to form plaques and small nodules, involving her face, anterior neck, upper chest, bilateral lateral upper arms, and upper back (Figure 1A-1D). No scale or crust was present. There were no oral ulcers, genital lesions or palmar and plantar rash or lymphadenopathy. She also complained of generalized malaise, fever, chills, arthralgia, and recent unintended 10-pound weight loss. Based on the clinical presentation, the differential diagnosis included cutaneous lupus erythematosus, Sweet's syndrome, cutaneous T-cell lymphoma, scleromyxedema, HIV and secondary syphilis.

A punch biopsy was performed on one of her left upper arm lesions, which revealed superficial and deep dermal predominantly perivascular and periadnexal inflammatory infiltrate (Figure 2A). Though the inflammatory infiltrate extended to the superficial subcutaneous adipose tissue, frank panniculitis was not seen. Within the deep dermis, there was an accentuation of the inflammatory infiltrate around several small caliber nerve fibers (data not shown). There was focal interface dermatitis with vacuolar changes of the basal keratinocytes and lymphocyte exocytosis (Figure 2B). The epidermis was slightly acanthotic with mild hyperkeratosis. An obvious Grenz zone was not observed. The inflammatory infiltrate was composed predominantly of epithelioid histiocytes with abundant amounts of pale eosinophilic cytoplasm and small ovoid nuclei, admixed

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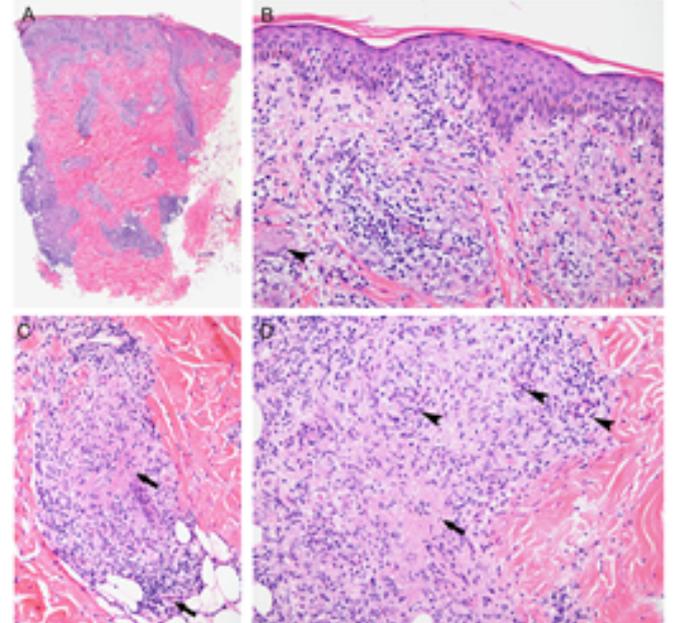
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**Figure 1:** Clinical appearance. Multiple, erythematous non-scaly papules, plaques and small nodules involving the (A) face, (B) upper arms, (C) anterior neck and upper chest, and (D) upper back.

with multinucleated histiocytes, lymphocytes and scattered plasma cells and eosinophils. Some of the blood vessels surrounded by the granulomatous inflammatory infiltrate demonstrated vascular endothelial swelling, and mononuclear lymphocytes could be identified within the thickened vessel walls (Figure 2C,D). In some of these foci, the blood vessel could not be identified and was replaced by fibrin and admixed with karyorrhectic cellular debris. Special stains were negative for acid fast bacilli and a Warthin-Starry stain failed to reveal unequivocal spirochetal organisms. A specimen was also sent to the Center for Disease Control and Prevention and an immunofluorescence study using anti-treponemal antibody revealed multiple spirochetes, confirming the diagnosis of secondary syphilis (data not shown).



**Figure 2:** Histopathologic features. Hematoxylin and eosin stained sections show (A) a superficial and deep dermal perivascular and periadnexal inflammatory infiltrate. (B) There is a mild interface dermatitis and perivascular lymphohistiocytic infiltrate with occasional multinucleated histiocytes (arrowhead). Perivascular granulomatous infiltrate with central fibrinous exudate and cellular debris (upper arrow); scattered eosinophils are also seen (lower arrow). (D) Endothelial swelling and mononuclear cells within vessel walls (arrowheads) and prominent fibrinous exudate around an inconspicuous vessel. Magnifications: A- 40 $\times$ , B-D- 200 $\times$ .

She ultimately admitted to intravenous drug abuse and engaging in unprotected sexually activity with her ex-husband during the past one year. She also recalled painful vaginal and oral lesions a while ago that had resolved by the time the rash erupted. An extensive laboratory work up including complete blood count, comprehensive metabolic panel, and serologic studies for anti-Smith, anti-RNP, anti-SSA, anti-SSB, anti-dsDNA antibodies, rapid plasma reagin (RPR), syphilis IgG antibody, and HIV serology was performed. All tests were within normal limits except for positive syphilis IgG antibody and RPR titer of 1:512. She was treated with one dose 2.4M units of benzathine penicillin intramuscularly. A day later, she developed sudden left-sided loss of vision and mental status changes and was diagnosed with left-sided anterior uveitis. A cerebrospinal fluid serology was performed and was found to be negative for neurosyphilis. Nevertheless, the patient received treatment with intravenous 4M units of aqueous crystalline penicillin G, every 4 hours for 14 days. The patient's neurologic symptoms were eventually attributed to her abusing pregabalin, diphenhydramine, and tramadol. Her skin rash had improved significantly on follow-up visit 2 weeks after discharge from the hospital. The visual loss in her left eye was improving at follow-up with her ophthalmologist, while conjunctival injection, pain and burning sensation had completely subsided.

## Discussion

Syphilis, particularly in its secondary stage has been notoriously referred to as the great imitator. The myriad clinical presentations of syphilis have been extensively documented in the past centuries. With the advent of antibiotics and more recently the HIV control programs, there was an overall decrease in the incidence of the disease towards

the turn of last century. With decreasing numbers of syphilis cases, the varied clinical phenotypes have been largely forgotten. However, during the past decade or so, there has been a steady rise in the number of reported cases of syphilis, especially in specific populations [1,2]. Moreover, this re-emerging infection, while not being in the list of common diagnoses, may present with unusual clinical and histologic phenotypes, making it a diagnostic challenge, particularly in low-risk populations.

Secondary syphilis usually develops 30 to 90 days after the appearance of chancre [9], and the most common presentation includes generalized skin rash, mucosal lesions and generalized or localized lymphadenopathy and is often associated with fever, malaise and weight loss [6]. Typical skin rash of early secondary syphilis include macular, small papular, follicular (pseudovesicular), lichenoid, vesicular, psoriasiform and corymbiform rashes [7]. Late secondary syphilis may present with large papules, condylomata lata, hypertrophic papules (frambesiform lesions) and also pustular, annular and rarely (ulcerating) nodular lesions. The cutaneous lesions are usually symmetrical with frequent facial involvement.

Granulomatous inflammation is a hallmark of tertiary syphilis, which also presents with massive caseating necrosis [10-13]. Though

uncommon, a prominent histiocytic inflammatory infiltrate has been described in lesions of secondary syphilis as well [11,14-17]. In most cases, the presence of mucosal ulcerations, involvement of palms and soles as well as genital lesions is usually the tip-off that raises the possibility of syphilis. In the absence of these hints, clinical diagnosis of atypical secondary syphilis can be challenging and in multiple instances, the patients may be treated for other diseases unsuccessfully.

The clinical differential diagnoses for a widespread erythematous, indurated papulo-nodular skin eruption is often long and comprises of cutaneous lymphoid hyperplasia, Sweet's syndrome, lymphoproliferative diseases (primary cutaneous lymphomas, secondary cutaneous involvement by a systemic lymphoma, leukemia cutis); other neoplasms including histiocytoses, metastatic melanoma or carcinoma; infections such as lepromatous leprosy, other mycobacterial infections and disseminated deep fungal infections; granulomatous processes such as disseminated granuloma annulare, sarcoidosis and connective tissue disorders such as scleromyxedema and lupus erythematosus [18].

Review of the English literature for cases of secondary syphilis with no mucosal or genital lesions and without involvement of palms and soles reveals that most of these cases were characterized by a prominent histiocytic inflammatory infiltrate (Table 1). In standing with the rate

Reference	Age / Sex	Duration (weeks)	Clinical presentation	Preceding genital lesions	Distribution	Lymphadenopathy	Histopathology	
							Pattern	Cellular components
Biro et al. 1968 [26]	52/M	12	Papules, plaques, nodules	None	Chest, back, shoulders	Axillary, postauricular, antecubital, inguinal	Perivascular infiltrate, non-necrotizing granuloma	Lymphocytes, plasma cells histiocytes
Baum et al. 1983 [21]	58/M	4	Papules, nodules	None*	Face, neck, chest, back, groin	None	Biopsy not performed	
Baum et al. 1983 [21]	59/M	> 3	Nodules	None	Neck, axillae, lower mid-back, inguinal areas	Not reported	Periadnexal, perivascular infiltrate, mild interface dermatitis	Lymphocytes, histiocytes, plasma cells, multinucleated histiocytes
Baum et al. 1983 [21]	52/M	< 2	Nodules	None*	Face, neck, chest, shoulders	Not reported	Biopsy not performed	
Hodak et al. 1987 [23]	66/M	8	Nodules	None	Face, neck, scalp, upper extremities, ear lobes	Cervical, axillary, inguinal	Dense mid- to deep dermal infiltrate with formation of follicles	Lymphocytes, histiocytes, eosinophils, neutrophils, plasma cells
Papini et al. 1998 [24]	23/M	4	Papules, plaques, nodules	Yes	Chest, abdomen	All superficial	Dense dermal infiltrate with perivascular accentuation, swollen endothelial cells, vessel wall infiltration by lymphocytes or plasma cells	Lymphocytes, plasma cells, histiocytes, multinucleated histiocytes, eosinophils
Fonseca et al. 1999 [22]	42/M	16	Plaques	None <sup>†</sup>	Face, trunk, extremities	None	Dense dermal infiltrate, non-necrotizing granulomas, perineural, perivascular accentuation, endothelial cell hyperplasia	Perivascular epithelioid and multinucleated histiocytes, lymphocytes, plasma cells
ul Bari and Raza 2006 [19]	29/F	3	Papules, nodules	None	Face	Cervical	Perivascular infiltrate	Plasma cells
Brar et al. 2007 [28]	28/M	4	Papules, plaques, nodules	None	Face, upper chest, back, upper extremities	Cervical, axillary, inguinal, epitrochlear	Dense dermal infiltrate, non-necrotizing granulomas	Epithelioid histiocytes, plasma cells, lymphocytes
Tsai et al. 2007 [29]	49/M	4	Plaques, nodules	None	Trunk, extremities, face	Cervical, axillary	Lichenoid dermatitis, and dense dermal perivascular and periadnexal, loose granulomas	Plasma cells, histiocytes, lymphocytes
Lanjouw et al. 2009 [30]	20/M	5	Papules, nodules	None	Face, trunk, extremities	Inguinal	Dense dermal infiltrate with perivascular accentuation, non-necrotizing granulomas	Lymphocytes, plasma cells, eosinophils, histiocytes, multinucleated histiocytes
Moon et al. 2009 [20]	38/M	26	Single nodular plaque	None	Left areola	None	Dense dermal infiltrate with formation of follicles, exocytosis and granulomatous infiltrate	Heavy lymphohistiocytic infiltrate, eosinophils, neutrophils, plasma cells
Jang et al. 2011 [25]	46/M	4	Single nodule	None	Scalp	Not reported	Dermal interstitial infiltrate with perivascular and periadnexal accentuation	Lymphocytes, plasma cells

Glatz et al. 2013 [15]	21/F	8	Patches, ulcerated nodules	None	Face, neck, upper trunk, upper arms	None	Interface dermatitis, non-necrotizing granulomas	Non-necrotizing granulomas, multinucleated histiocytes, eosinophils, plasma cells
Liu and Ma 2014 [27]	32/M	12	Papules, nodules	None	Face, trunk, extremities	None	Dense dermal infiltrate	Plasma cells, lymphocytes, histiocytes, multinucleated histiocytes
Rysgaard et al. 2014 [16]	62/M	< 2	Papules, nodules	None*	Trunk, upper extremities	Not reported	Perivascular and periadnexal infiltrate, non-necrotizing granuloma	Histiocytes, lymphocytes, plasma cells
Current case	44/F	4	Papules, plaques, nodules	Yes	Face, neck, chest, back, upper extremities	None	Perivascular infiltrate, focal interface dermatitis, endothelial swelling and focal vasculitis	Histiocytes, lymphocytes, rare plasma cells and eosinophils, multinucleated histiocytes

**Table 1:** Previously reported cases of secondary syphilis with no mucosal ulcers, genital lesions or palmar / plantar involvement. \* Prior history of treated syphilis, ¥ history of HIV

of reported cases of syphilis, there was a male predominance with only 3 of the patients, including the current case being female [15,19]. In most patients, the duration of skin lesions before presentation was 12 weeks or less, with exception of one patient [20]. The lesions range from plaques to papules to nodules and are rarely ulcerated [15]. Face, upper trunk and upper extremities are the commonly affected areas, while lower back and intertriginous areas are rarely affected [21]. In most patients, the rash was either asymptomatic or pruritic [22-24]; however, our patient complained of associated pain. While most patients presented with multiple skin lesions, two patients presented with single isolated lesions, which makes the diagnosis almost impossible without histologic examination and a high-degree of suspicion [20,25]. Lymphadenopathy was not a standard feature and less than half of the patients were reported to have any lymph node enlargement. Three patients had prior history of previously treated syphilis [16,21], while one had recently been diagnosed with HIV and hepatitis C [22]. Most of the patients did not display other signs of secondary syphilis. However, 3 patients, including ours had unilateral or bilateral uveitis [22,26], while 2 patients had generalized maculopapular rash before the development of papules and nodules [21,27]. One patient had flu-like symptoms before development of cutaneous lesions [28]. While the typical moth-eaten pattern of alopecia was not noted in any of the patients, lateral alopecia of the eyebrows, complete loss of eyebrows and alopecia of eyelid margins were seen [19,22,28].

Biopsies were performed in all patients except two patients that had a prior diagnosis of syphilis and many of these patients were at low-risk for sexually transmitted diseases. Perivascular infiltrate of epithelioid histiocytes, admixed with varying numbers of lymphocytes, plasma cells and multi-nucleated histiocytes was the most common histologic feature. While at least scattered plasma cells were seen in all cases, prominence of plasma cells was noted in only 2 cases [19,25]. Rarely, dense dermal lymphocyte-predominant inflammatory infiltrate with formation of follicles may be seen and were diagnosed as pseudolymphomatous processes [20,23].

The histiocytes frequently formed loose, non-necrotizing granulomas around the dermal vasculature. In most cases, neither the blood vessels, nor the endothelial cells were affected. However, in some cases including ours, there was endothelial swelling, hyperplasia and mononuclear cells within vessel walls. Though frank vasculitis may not be evident, perivascular fibrinous exudate, admixed with cellular debris may simulate necrosis. Perineural inflammation was seen only in one case, due to which it was initially misdiagnosed as leprosy [22]; in our case, there was perineural accentuation of the inflammatory infiltrate. In some cases, histiocytes were inconspicuous [19,25-30].

Granulomatous inflammatory infiltrate is considered to be an

indicator of early secondary syphilis and most patients with exception of two presented within 12 weeks of onset of their skin lesions [16]. In the late stages, after resolution of the inflammation, pigmentary alterations may predominate [7]. Nevertheless, with the re-emergence of syphilis, it is important to remember syphilis as a possibility in unusual clinical scenarios, especially because of the relative ease of treatment. It should be included in the list of clinical differential diagnoses of disseminated erythematous and indurated papulo-nodular cutaneous lesions, even in the absence of risk factors and other characteristics of typical secondary syphilis, such as palmar / plantar involvement, mucosal lesions, lymphadenopathy or papulosquamous eruption.

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