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CASE REPORT

Nodular secondary syphilis in a woman

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glatz.martin@gmx.net**SUMMARY**

We report the case of a 21-year-old woman with symmetrically distributed, ulcerated nodules and plaques on the face, neck and arms. Initial differential diagnoses included pyoderma or sarcoidosis based on the clinical presentation and histopathology with non-caseating granulomas. After inefficient treatment with topical and systemic fusidic acid and steroids, we diagnosed nodular secondary syphilis owing to positive serology and immunohistochemical staining of *Treponema pallidum* in lesional skin. After treatment with benzathine penicillin, skin lesions improved and antibody titres declined significantly within 3 months. Nodular skin lesions in secondary syphilis are rare with 15 reported cases within the last 20 years. Furthermore, the granulomatous histology is often misleading. Our patient's case suggests that the physicians should be aware of syphilis as a possible differential diagnosis also in patients outside a high-risk population for sexually transmitted diseases and with an unusual clinical presentation.

BACKGROUND

Since the late 1990s, the incidence of syphilis in Western Europe is increasing especially among men having sex with men.^{1 2} Secondary syphilis usually develops 5–12 weeks after infection with the

causative agent *Treponema pallidum* owing to haematogenous dissemination of the spirochete.^{3 4} Known as the 'Great imitator',⁵ secondary syphilis often mimics various diseases; therefore, clinical diagnosis can be difficult. Early stages of secondary syphilis are generally characterised by many small and symmetrically distributed efflorescences; whereas in later stages lesions increase in size, but decrease in number and concentrate on a particular body site.³ The most frequently described type of efflorescences are macules or maculopapules, whereas plaques and nodules like in our patient are rare.^{4 6} In case of ulcerated skin lesions, differentiation between secondary and tertiary syphilis may be even more challenging. Here, we report a rare presentation of a secondary syphilis with ulcerated nodules and plaques on the face, neck and upper trunk in a patient outside a high-risk population for syphilis.

CASE PRESENTATION

A 21-year-old Swiss female clerk, residing since her birth in a countryside village in the canton of Zurich, presented with painless red patches and scaling, ulcerated, weeping nodules of up to 2 cm in diameter. The skin lesions were symmetrically located in the face, neck and upper parts of the



Figure 1 Clinical images of the 21-year-old patient. (A) Erythematous patches, papules and plaque-like skin lesions in the face. (B) Excoriated plaques on the neck. (C and D) Almost completely resolved skin lesions in the face and on the neck 3 months after therapy.

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trunk and arms (Figure 1). Mucous membranes, palms and soles were not affected, and regional lymphadenopathy was absent. Aside skin lesions, the patient suffered from headache, but without systemic symptoms such as fever, malaise or weight loss. Two months before the visit to our clinic and soon after the onset of symptoms, a private dermatologist diagnosed a pyoderma on grounds of the inflammatory aspect of skin lesions and the detection of Staphylococci by the cultivation of skin swabs taken from the facial nodules and the nasal vestibule. Because the treatment with topical and systemic fusidic acid did not improve skin lesions, a histological examination of two lesional punch biopsies was performed. Histopathology showed inflammatory infiltrate at the dermoepidermal junction (interface dermatitis) and non-caseating (ie, non-necrotising) granulomas in the whole dermis with multinucleated giant cells, eosinophil leucocytes and plasma cells. Standard and specific stainings (PAS, Brown-Brenn-Gram, Ziehl-Neelsen) did not reveal fungal, bacterial or mycobacterial infection. Based on histopathology with granulomas, a cutaneous sarcoidosis was proposed and treatment with oral corticosteroids initiated. With that, skin lesions slightly improved, but steroids had to be aborted owing to adrenal insufficiency (fasting cortisol 100 nmol/l). Because skin lesions persisted, the patient was presented to our clinic.

INVESTIGATIONS

Owing to the clinical presentation with symmetrically distributed skin lesions and according to the standardised diagnostic workup procedures of our clinic, we suspected syphilis. The patient reported to be in a stable heterosexual relationship, and having had sexual contact with two clinically healthy men within the last 2 years before the onset of symptoms. She could not recall genital, anal or oropharyngeal ulceration prior to current symptoms. A screening for sexually transmitted infections revealed the following results: *T pallidum* particle agglutination test (TPPA) 1:327 680, venereal disease research laboratory (VDRL) test 1:16, anti-*T pallidum* IgM-ELISA index 1.32 (negative <0.90); HIV 1/2 and hepatitis B/C negative. A lumbar puncture excluded neurosyphilis with a TPPA of 1:80 (caused by high serum TPPA), negative VDRL, normal cell count and absence of oligoclonal bands. We re-examined the previous histopathology owing to serology results and performed an immunohistochemical staining for treponemal epitopes (*T pallidum* antibody 1:100; Biocare Medical, Dietikon, Switzerland) what led to direct detection of *T pallidum* in the dermis (Figure 2). We diagnosed a nodular secondary syphilis based on positive *T pallidum* serology, histopathology with granulomas and many plasma cells and positive immunohistochemistry with direct detection of *T pallidum* in lesional skin.

DIFFERENTIAL DIAGNOSIS

Clinical presentation and presence of non-necrotising granulomas resembled sarcoidosis, for which the patient was initially treated, though plasma cells are not a characteristic finding in sarcoidosis. Furthermore, a systemic sarcoidosis was unlikely owing to unremarkable physical examination of lymph nodes, normal chest radiography and abdominal ultrasound.

Tuberculosis is a granulomatous disease, and therefore a differential diagnosis. In contrast to the case presented here, tuberculosis is characterised by necrotising granulomas. It was excluded by negative direct detection of *Mycobacterium tuberculosis* with Ziehl-Neelsen staining and PCR from skin biopsy samples. Pulmonary tuberculosis was unlikely owing to normal chest radiography.

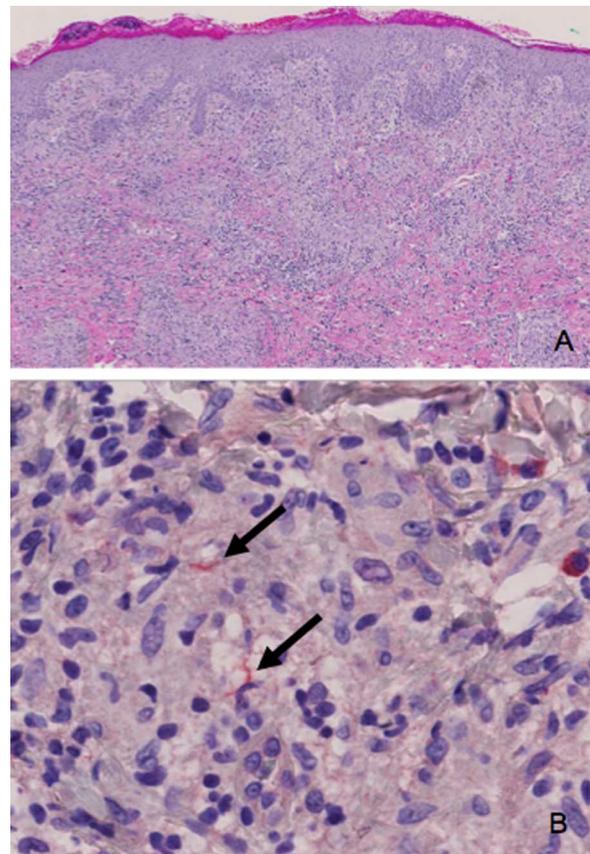


Figure 2 Histopathological images of a punch biopsy from a nodular skin lesion at the right upper arm (clinical images not shown). (A) H&E staining, magnification $\times 40$. Hyperkeratosis, acanthosis and spongiosis of the epidermis with focal erosion. Interface dermatitis with a diffuse interstitial and perivascular lymphohistiocytic cellular dermal infiltrate and non-caseating granulomas. (B) Immunohistochemical staining for *Treponema pallidum*. Arrows indicate two *T pallidum* spirochetes in the dermis.

Clinically, the exanthema of the patient resembled Yaws, which is a non-venereal treponematoses caused by *Treponema pertenue* endemic in the Southern hemisphere.⁷ Because the patient never visited a Yaws-endemic region and missed other characteristic signs such as annular scaly macules or hyperkeratotic plaques on palms and soles, we excluded this diagnosis.

A foreign body reaction, another possible histological differential diagnosis, was excluded by normal polarised light microscopy.

TREATMENT

Because of the unknown duration of syphilis, it was impossible to exclude a late-stage syphilis. Therefore, we decided for a treatment with three consecutive weekly injections of 2.4 million units benzathine penicillin. Prior to the first dose of penicillin, we administered 50 mg prednisone to prevent a Jarisch-Herxheimer reaction.

OUTCOME AND FOLLOW-UP

The patient was seen for clinical and serological controls 1 and 3 months after the end of the therapy. Within 3 months after therapy, the skin lesions almost completely resolved (Figure 1). VDRL declined to 1:4, and IgM became negative. More than fourfold decline in the non-treponemal test results in combination with the seronegativity of IgM is a serological indicator for the treatment success.^{8,9}

DISCUSSION

Secondary syphilis frequently presents with macules and papules on the trunk, face and extremities. The presence of big nodules and plaques that are partly ulcerated is a rare manifestation of secondary syphilis. About 15 cases of secondary syphilis with big nodules and plaques resembling those of our patient's have been reported within the last 20 years (Table 1). These cases shared some similarities with our case presentation. The big nodules and plaques had sometimes a granulomatous aspect and preferably appeared at the upper half of the body, especially the

head and neck region. Palms and soles, otherwise typically affected in secondary syphilis, were usually spared in these patients, and the mucous membranes were regularly spared. Histopathology was characterised by caseating or non-caseating granulomas, many lymphocytes and plasma cells in the dermis. Owing to clinical appearance and histopathology many patients were initially diagnosed with lymphoma¹⁰⁻¹³ or granulomatous diseases such as sarcoidosis.¹³ Eventually, the diagnosis of syphilis was substantiated by serology with positive non-treponemal and treponemal-specific tests in all cases. Antibiotic treatment

Table 1 Patients with nodular secondary syphilis reported 1992–2012

Reference	Patient (Age, gender)	Localization of skin lesions	Affection of palms or soles	Affection of mucosal membranes	Histopathology	Serology	HIV status	Treatment
Rosmaninho ¹²	64, male	Neck, arms, back	No	No	Histiocytes, plasma cells	VDRL 1:512 TPHA pos	Positive	3× benzathine penicillin 2.4 M units
Jang ¹¹	46, male	Scalp	No	No	Plasma cells, lymphocytes	VDRL 1:128 TPHA pos FTA pos	Negative	1× benzathine penicillin 2.4 M units
Brar, <i>Indiana J Dermatol Venereol Leprol</i> 2007;73:437	28, male	Face, arms chest, back	No	No	Plasma cells, lymphocytes Non-sarcoidal granulomas	VDRL 1:512 TPHA pos	Negative	3× benzathine penicillin 2.4 M units
Breznik ¹³	52, male	Face, upper trunk, feet	Yes (soles)	No	Plasma cells, lymphocytes, granulomas	VDRL 1:1024 TPHA 1:40960 FTA pos	Negative	3× benzathine penicillin 2.4 M units
ul Bari ¹⁰	29, female	Forehad	No	No	Plasma cells	VDRL 1:512 TPHA 1:64	Negative	2× benzathine penicillin 2.4 M units
Dinotta, <i>G Ital Dermatol Venereol</i> 2009;144:725	29, male	Scrotum, penis	No	No	N/A	N/A	N/A	Diaminopenicillin
Battistella ¹⁹	33, male	Face, arms, trunk, feet, genital region	No	No	Plasma cells, lymphocytes	VDRL 1:64 TPHA 1:10260	N/A	3× benzathine penicillin 2.4 M units
Tsai, <i>J Am Acad Dermatol</i> 2007;57:557	49, male	Face, arms trunk	No	No	Plasma cells, lymphocytes, granulomas	Plasma reagin 1:128 TPHA pos	Negative	2× benzathine penicillin 2.4 M units
Pandhi, <i>J Eur Acad Dermatol Venereol</i> 2005;19:256	35, male	Face, arms trunk, legs	No	No	Plasma cells, giant cells	VDRL 1:128 TPHA pos	Negative	2× benzathine penicillin 2.4 M units
Engel ¹⁸	34, female	Face, eyes, arms, trunk, legs	No	No	Plasma cells granulomas,	VDRL 1:512 TPHA 1:163840	Negative	Penicillin intravenous 10 M units three times a day for 4 weeks
Dave, <i>Dermatol Online J</i> 2003;9:9	22, male	Face, arms, trunk, legs	No	No	Granulomas	VDRL 1:64 TPHA pos	Negative	1× benzathine penicillin 2.4 M units
Harden, <i>Arch Dermatol</i> 1997;133:1027	39, male	Scalp, face, neck	No	No	Plasma cells	Plasma regain 1:128 TPHA pos	N/A	N/A
Papini, <i>Br J Dermatol</i> 1998;138:704	23, male	Trunk, arms, legs	No	No	Sarcoidal granulomas	VDRL pos TPHA 1:5120 FTA pos	Negative	3× benzathine penicillin 2.4 M units
Adriaans, <i>Arch Dermatol</i> 1992;128:978	40, male	Arms, legs, penis	No	No	Plasma cells, granulomas	VDRL 1:256 TPHA pos	N/A	N/A
Glatt, <i>Clin Infect Dis</i> 1996;23:231	29, male	Arms, feet	Yes	No	Plasma cells	VDRL 1:64 FTA pos	Positive	3× benzathine penicillin 2.4 M units, Doxycycline 100 mg twice daily for 1 month

FTA, fluorescent treponemal antibody; N/A, not available; TPHA, *Treponema pallidum* haemagglutination assay; VDRL, Venereal Disease Research Laboratory

with three injections of benzathine penicillin led to healing of skin lesions and a decrease of VDRL within a few months.

In our patient, the diagnosis of syphilis was confirmed by the direct detection of *T pallidum* in lesional skin with immunohistochemistry.¹⁴ The visualisation of spirochetes in skin biopsies with common methods such as dark field microscopy and silver staining is difficult, whereas immunohistochemical methods seem to be more sensitive in all stages of syphilis.^{15–16} The discrimination between secondary and tertiary syphilis is challenging in the case of ulcerating nodules and plaques. A tertiary syphilis is characterised by usually unilateral, deep ulcerating nodules with necrotising granulomas (gummas).¹⁴ Our patient had skin lesions that were distributed on both body sites and were not deeply ulcerated, similar to the previously reported cases of secondary syphilis.^{12–17–19} Furthermore, histopathology showed non-necrotising granulomas and an interface dermatitis, which are the characteristics of secondary syphilis.²⁰ Therefore, we tended to the diagnosis of a secondary syphilis in our patient. Plasma cells can be found in both syphilis stages.^{20–21} Serological findings did not aid in the decision for secondary or tertiary syphilis in this case. A recently published study on a large population of primary- to third-stage syphilis patients has shown that intermediate level VDRL (1:16) and ELISA IgM (1.32) and a high TPPA (1:327 680) like in our patient do not differentiate between both disease stages.⁸

The performance of a lumbar puncture in our patient was against the current recommendations. We decided for the lumbar puncture owing to enduring cephalgia and after thorough discussion of this issue with the patient. Although results excluded neurosyphilis, this invasive procedure was in retrospective not necessary in our patient as shown in a recent study. In this study, lumbar punctures were performed in 70 untreated, HIV-negative patients with latent syphilis of which 11% had mild neurological signs similar to our patient, but none of the test results met the diagnostic criteria for neurosyphilis.²² Therefore, lumbar puncture is not considered to be a standard of care procedure and should be strictly indicated according to current guidelines. These guidelines recommend lumbar puncture in patients with positive syphilis serology and (i) clinical neurological symptoms, (ii) clinical ocular or otological symptoms and (iii) concomitant HIV infections.²³

In conclusion, we report a rare case of nodular secondary syphilis in a heterosexual female patient outside a high-risk population of sexually transmitted diseases. This case also demonstrates the possible difficulties in differentiating secondary- from tertiary-stage of syphilis based on clinical and serological findings.

Learning points

- ▶ Symmetric distributed nodules and plaques in the face and upper parts of the trunk are a rare, but a possible manifestation of secondary syphilis.
- ▶ Secondary syphilis should be included in the list of differential diagnoses in each patient with acute or subacute symmetric skin lesions.
- ▶ These skin lesions in secondary syphilis may histologically resemble lymphoma or granulomatous diseases such as sarcoidosis.
- ▶ Even individuals outside a high-risk population for sexually transmitted infections (eg, heterosexual women from the countryside) and without a striking personal history may be diagnosed with venereal diseases.

Contributors MG participated in the patient's care, reviewed the previous literature and wrote the majority of the original draft of the manuscript. YA participated in writing of the original draft of the manuscript, reviewed the previous literature and critically reviewed the submitted version of the manuscript. KK was responsible for histopathology and immunohistochemistry, wrote the histological part of the manuscript and critically reviewed the submitted version of the manuscript. PB gave essential advice for the interpretation of serology during diagnosis and follow-up, wrote the serological part of the manuscript and critically reviewed the submitted version of the manuscript. AC was responsible for the patient's care, planned the case report and critically reviewed the submitted version of the manuscript.

Competing interests None.

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