

Received: 2017.09.14
Accepted: 2017.12.10
Published: 2018.03.04

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 238-243
DOI: 10.12659/AJCR.907127

Secondary Syphilis with Tonsillar and Cervical Lymphadenopathy and a Pulmonary Lesion Mimicking Malignant Lymphoma

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 27
Final Diagnosis: Secondary syphilis
Symptoms: Fever • loss of appetite • neck mass • night sweats • weight loss
Medication: Oral amoxicillin
Clinical Procedure: Lymph node biopsy
Specialty: Infectious Diseases

Objective: Challenging differential diagnosis




Background: Syphilis is a sexually transmitted disease caused by the pathogen *Treponema pallidum*. Prevalence continues to rise, especially among men who have sex with men (MSM). Due to changes in patterns of sexual activity, manifestations of the disease are highly variable.

Case Report: A 27-year-old male visited the hospital for a low-grade fever and tender 5-cm mass in the right side of his neck. His right tonsil was swollen and covered with a white coating. Levofloxacin was prescribed, but ineffective. The patient's levels of liver function enzymes increased gradually. Systemic magnetic resonance imaging (MRI) revealed bilateral cervical lymphadenopathy with right predominance, a right pulmonary nodule, and a periportal lymph node, suggestive of malignant lymphoma. However, a biopsy of the right cervical lymph node showed nonspecific inflammation. Preoperative rapid plasma reagin (RPR) and *T. pallidum* latex agglutination (TPLA) tests were positive. The patient was MSM and reported oral sex with many sexual partners. A diagnosis of secondary syphilis was made. Oral amoxicillin was effective, and all symptoms other than periportal lymph node resolved.

Conclusions: Tonsillitis, cervical lymphadenopathy, and lung lesions can be manifestations of secondary syphilis. A detailed history, pathology, and serology are crucial for diagnosis.

MeSH Keywords: Homosexuality, Male • Liver • Lung • Lymph Nodes • Syphilis

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/907127>

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Background

Syphilis is a sexually transmitted disease (STD) caused by *Treponema pallidum* [1] that presents in four infection stages: primary, secondary, latent, and tertiary. Primary syphilis is a painless, solitary, indurated ulcer with a clean base (“chancre”) at the inoculation site, most often in genital and anal areas, which disappears without treatment. Secondary syphilis appears typically as a skin rash, which resolves spontaneously. Secondary syphilis may also manifest as mucosal lesions, diffuse lymphadenopathy, hepatosplenomegaly, hepatitis, and/or nephrotic syndrome. Latent syphilis, including early- and late-stage disease, is defined by a lack of clinical symptoms. Tertiary syphilis includes cardiovascular syphilis, late neurosyphilis, and gummatous syphilis presentations. Primary, secondary, and early latent stages are referred to as infectious syphilis and represent the targets of public health control. Syphilis has been called the great imitator because its manifestations resemble those of various other diseases.

Prevalence of syphilis in the general population (including men who have sex with men (MSM) in the USA and western Europe was relatively low in the 1980s and early 1990s [2]. Since then, however, the prevalence has continued to rise among MSM, especially among those who are human immunodeficiency virus (HIV) positive [2,3]. Because of changes in patterns of sexual activity, the clinical presentation of the condition is highly variable, rendering early detection and correct diagnosis difficult [4].

Here we describe a case of an MSM patient who presented with tonsillitis, cervical lymphadenopathy, and a pulmonary

lesion. The patient was diagnosed with secondary syphilis, for which detailed inquiries on sexual activities and serological tests were crucial.

Case Report

An otherwise healthy 27-year-old Japanese male noticed a painless swelling on the right side of his neck. It had been enlarging gradually and had become painful. A low-grade fever ensued. The patient also reported mild night sweats and loss of appetite and body weight (–2 kg) over the past month. Oral levofloxacin 500 mg/day and loxoprofen 60 mg as necessary were prescribed. The patient was referred to our hospital for further evaluation.

The patient smoked five cigarettes a day between the ages of 18 and 22, and drank 3 liters of beer three times a week. He never abused illegal substances. He had a cough and yellow sputum. His body temperature was 37.2°C. Physical examination revealed that the patient’s right tonsil was swollen, reddish and markedly white-coated, which suggested infectious tonsillitis. He had a soft, tender mass in the right side of his neck (5×3×1 cm). No lymph nodes were palpable in the supraclavicular, axillary, or inguinal areas. He did not have hepatosplenomegaly or neurological disturbances. Laboratory tests showed a high C-reactive protein (CRP) level as well as mildly elevated aspartate transaminase (AST) and alanine aminotransferase (ALT) levels (Table 1). Levofloxacin was continued. One week later, the patient’s CRP rose further to 4.2 mg/dL, and various liver function tests showed elevation [AST 40 IU/L,

Table 1. Summary of the patient’s initial laboratory data.

Parameter	Value	Normal range	Parameter	Value	Normal range
White blood cells	6,760 cells/ μ L	3,500–9,000	AST	35 IU/L	10–33
Monocyte	7.7%	2.0–11.0	ALT	46 IU/L	4–30
Lymphocyte	12.9%	19.0–49.0	ALP	320 IU/L	167–345
Basophil	0.9%	0.0–3.0	γ -GTP	70 IU/L	10–75
Eosinophil	1.6%	0.0–5.0	BUN	7 mg/dL	8–20
Neutrophil	76.9%	37.0–72.0	Creatinine	0.8 mg/dL	0.6–1.1
Hemoglobin	15.4 g/dL	14.0–18.0	Na	141 mEq/L	135–145
MCV	90.1 fL	80.0–100.0	K	4.0 mEq/L	3.4–5.0
Platelets	25.5×10^4 / μ L	12.0–36.0	Cl	104 mEq/L	98–108
Albumin	4.1 g/dL	3.9–4.9	CRP	3.2 mg/dL	0.0–0.4
LDH	182 IU/L	100–230	sIL-2R	1,020 U/mL	145–519

ALP – alkaline phosphatase; ALT – alanine aminotransferase; AST – aspartate transaminase; BUN – blood urea nitrogen; CRP – C-reactive protein; γ -GTP – γ -glutamyltransferase; LDH – lactate dehydrogenase; MCV – mean corpuscular volume; sIL-2R – soluble interleukin-2 receptor.

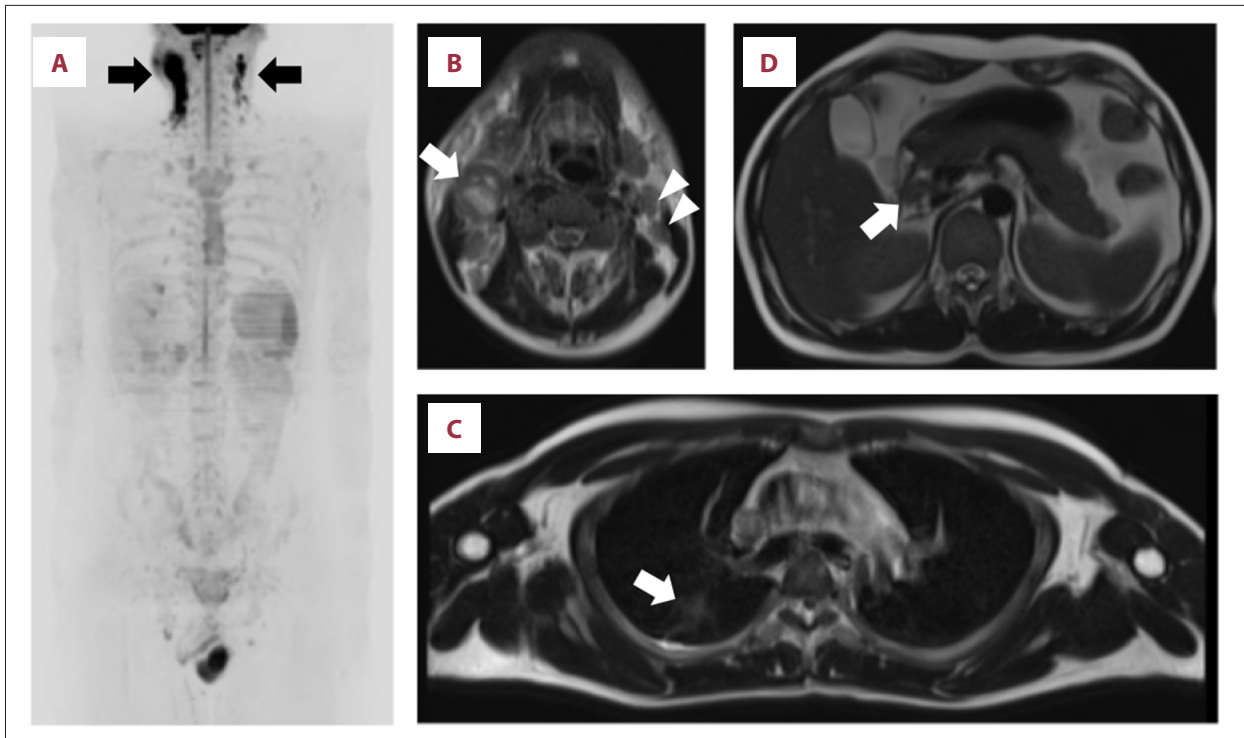


Figure 1. Systemic diffusion magnetic resonance imaging (MRI). (A) Whole-body image. Arrows show bilateral lymphadenopathy with right predominance. (B) Cervical lymph nodes. Central necrosis can be seen in the largest lymph node in the right neck (arrow). Arrowheads mark smaller lymph nodes in the left neck. (C) A nodule in the right lung (arrow). (D) A periportal lymph node (arrow).

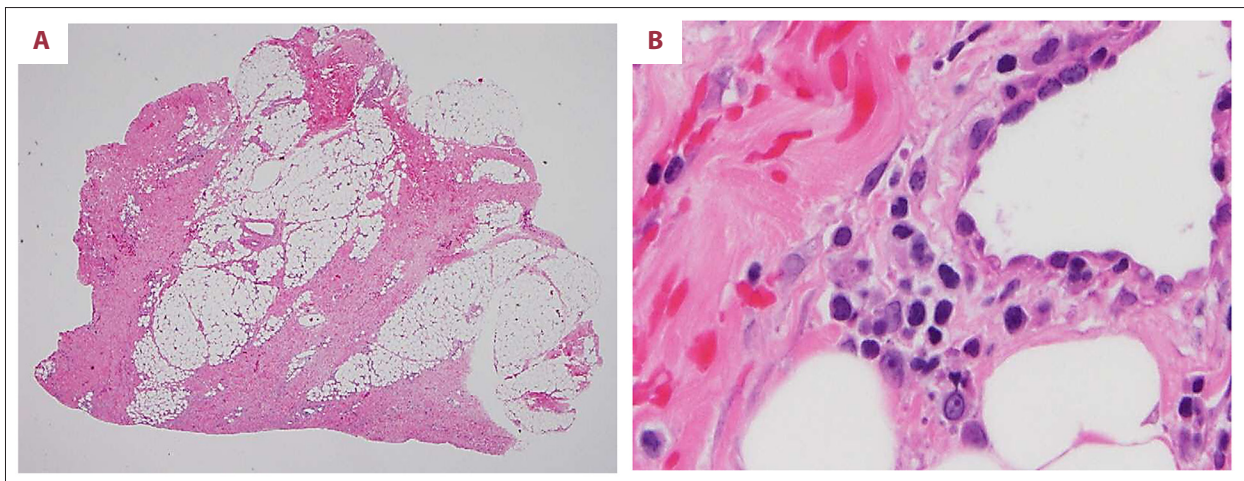


Figure 2. Histopathology of the cervical lymph node. (A) Low magnification. The tissue consists of adipose tissue with fibrosis. Hematoxylin and eosin (H&E) stain. Original magnification, 40 \times . (B) Blood vessels surrounded by lymphocytes with mildly expanded nuclei. H&E stain. Original magnification, 400 \times .

ALT 64 IU/L, alkaline phosphatase (ALP) 398 IU/L, γ -glutamyl-transferase (γ -GTP) 120 IU/L]. His soluble interleukin-2 receptor (sIL-2R) level was 1,020 U/mL.

The patient reported high fever (38°C) several days earlier. The right cervical mass hardened but did not change in size.

Levofloxacin was judged to be ineffective and discontinued (it had been taken for nine days in total). Systemic-diffusion magnetic resonance imaging (MRI) was taken to evaluate systemic lymphadenopathy considering malignant lymphoma. It showed bilateral cervical lymph nodes with right predominance (Figure 1A, 1B), a 2-cm nodule in the right lung (Figure 1C),

and a periportal lymph node (Figure 1D) with diffusion restriction. Hepatosplenomegaly was not detected.

The patient was scheduled for lymph node biopsy. Routine preoperative blood tests were positive for rapid plasma reagin (RPR) and *T. pallidum* latex agglutination (TPLA). Quantitative RPR was 67.3 RPR Unit (RU). Hepatitis B surface antigen, hepatitis C virus antibody, and HIV antigen/antibody titers were all negative. The patient was diagnosed with syphilis. He was MSM and had had oral sex with many sexual partners. He had never had a penile ulcer or skin rash. Lymph node biopsy was performed. The lymph node had a hard capsule, which precluded total excision. Oral amoxicillin 1,500 mg/day was prescribed to treat the syphilis infection while waiting for histopathological diagnosis of the lymph node. The patient was discharged two days later.

Histopathology revealed that the lymph node consisted of adipose tissue with fibrosis (Figure 2A). Connective tissue showed infiltration by lymphocytes (Figure 2B). The presence of lymphocytes with mildly expanded nuclei surrounding some blood vessels suggested nonspecific inflammation (Figure 2B). Neither silver stain nor Warthin-Starry stain revealed spirochetes. Southern blotting showed no recombination of immunoglobulin heavy chains, which rendered malignant lymphoma unlikely.

After two weeks of amoxicillin treatment, the patient's cervical lymph nodes had regressed markedly and flattened. He was afebrile. CRP and liver function test results decreased or remained within normal limits (CRP 0.1 mg/dL, AST 29 IU/L, ALT 54 IU/L, ALP 323 IU/L, γ -GTP 81 IU/L). RPR was lowered to 7.9 RU, and sIL-2R decreased to 562 U/mL. Systemic diffusion MRI performed three weeks after starting amoxicillin treatment demonstrated regression of cervical lymph nodes (Figure 3) and disappearance of the pulmonary nodule. However, the periportal lymph node persisted. Thereafter, he was lost to follow-up. Based on the history of oral sex with partners, positive serological tests, and effectiveness of amoxicillin, a final diagnosis of secondary syphilis was made.

Discussion

Here we presented a case of a young MSM with cervical lymphadenopathy, pulmonary nodule, and periportal lymph node, who was diagnosed with secondary syphilis. Reports on luetic cervical lymphadenopathy and oropharyngeal syphilis are increasing, possibly due to the prevalence of oral sex among MSM, although not all references mention sexual history in detail [5-8], and patients may deny a history of oral sex [9,10]. Cervical lymphadenopathy is commonly associated with tonsillitis [4,8,11] and oropharyngeal mucosal lesions

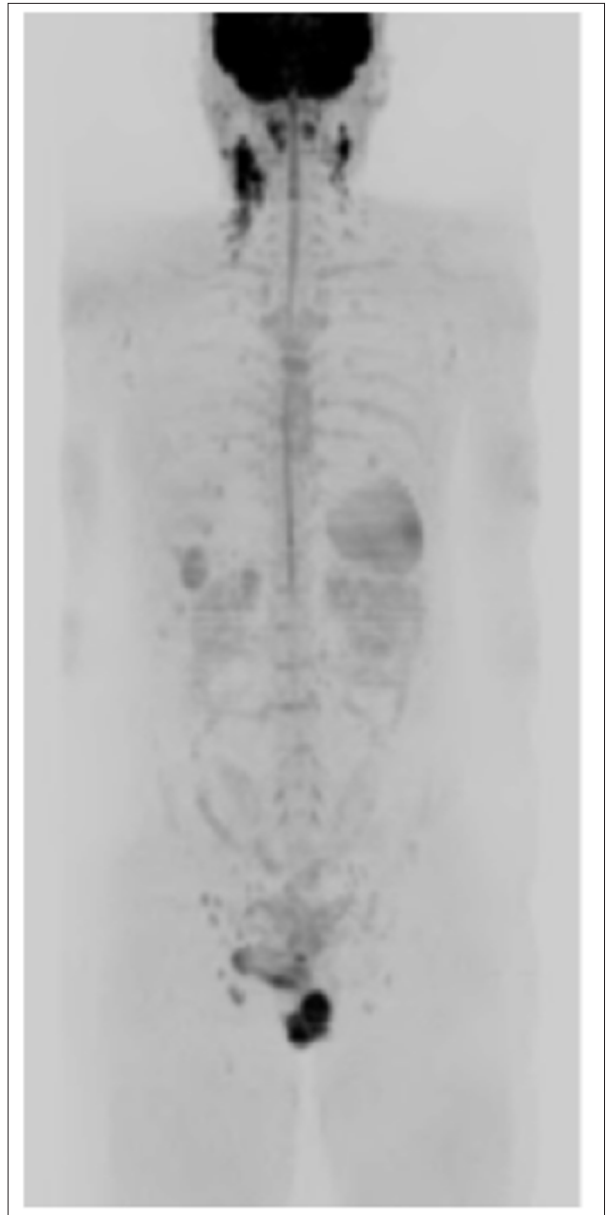


Figure 3. Systemic diffusion magnetic resonance imaging (MRI) after amoxicillin treatment. Cervical lymph nodes are diminished.

(ulcers in the lip [12,13], oral mucosa [13], tongue [12], and tonsils [8,11]). In patients with oropharyngeal syphilis, an extragenital chancre might go unnoticed [13]. Patients may lack typical symptoms of secondary syphilis (skin rash and condyloma lata), which delay diagnosis [13]. Differential diagnosis for cervical lymphadenopathy include infectious diseases (tuberculosis, toxoplasmosis, HIV infection, cat-scratch disease, Lyme disease, and rubella), autoimmune disease, nasopharyngeal/tonsillar carcinoma with metastasis, and malignant lymphoma [9,10]. Differential diagnosis for tonsillitis includes infectious mononucleosis and group A streptococcal infection.

Pulmonary lesions of syphilis (pulmonary syphilis; PS) have been reported, but rarely [5,6,14–16]. Coleman proposed clinical criteria for the diagnosis of secondary luetic involvement of the lung [17]. Patients can either be asymptomatic, as in the present case [5,6], or manifest respiratory symptoms such as dry cough [7], productive cough [15], and chest pain [14,16]. Thus, the likelihood of PS could be underestimated without systemic imaging evaluation. Radiographical images of PS show nodules with/without cavitation [5,6,14–16], subpleural consolidation [7,15], and interstitial infiltrates [6]. Bronchial biopsy [15], percutaneous needle aspiration [14], and excisional lung biopsy [14,16] are used for diagnosis. Bronchial washing and subsequent immunohistochemistry can reveal the presence of *T. pallidum* [15].

Secondary syphilis can also affect the liver. Freitas et al. reported a case of secondary syphilis with cholestatic hepatitis (“syphilitic hepatitis”) [7]. Mild cholestasis [4], elevated liver enzymes (such as γ -GTP and ALT [14], and transaminases [15]) and hepatosplenomegaly [4] might be observed. Pathological swelling of deep lymph nodes has been reported in patients with pancreatic lymphadenopathy [14]. The periportal lymph node in our case did not shrink during the short observation period following amoxicillin treatment; therefore, it is not clear whether it was caused by syphilis.

Differential diagnosis of syphilitic lymphadenopathy based on imaging is often confusing. MRI shows homogenous and high signal intensity on T1-weighted images [8,9]. Diffusion MRI, as in our case, and ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography [4,5,14] are both useful for screening and qualitative evaluation of malignancy, but cannot always distinguish inflammation from malignancy. Indeed, in one case report, standardized uptake values of fluorodeoxyglucose in syphilitic pulmonary nodules ranged from 4.37 to 5.59, suggesting malignancy [14]. Cystic changes resembling central necrosis may be observed in luetic lymph nodes [8]. Thus, large cervical lymph nodes and disseminated lymphadenopathy due to secondary syphilis can mimic multiple metastases of cancer.

Histopathological examinations are performed to rule out malignancy. In luetic tissues, plasma cell-rich inflammation is characteristic, regardless of the site of biopsy (e.g., tongue [18], palatine [18], tonsils [11,18], cervical lymph nodes [4,8,11,19], lung nodules [14,16], skin [16,18]). Fibrosis is observed in lung nodules [14] and the periphery of the swollen lymph nodes

(“capsular/parcel fibrosis”) [8,10,11,19]. Perivascular inflammation [6,8,12,19], occlusion vasculitis [8,19], multinucleated giant cells [8,19], and granuloma formation [8,10] can also be seen in various biopsy samples. None of these phenomena, however, are pathognomonic. Silver stains such as Dieterle and Warthin-Starry stain [10,18] can demonstrate the presence of bacterial bodies. Immunohistochemistry/immunocytochemistry using a specific antibody [8,18] and polymerase chain reaction targeting the 47-kD major lipoprotein immunogen [10,15] or DNA polymerase A gene [18] are reliable methods to prove the presence of *T. pallidum*. Without suspicion of syphilis and these specific tests, cytological or histological examinations of syphilitic lesions often lead to a diagnosis of nonspecific inflammation [4,6,9,10] or reactive (follicular) hyperplasia [4,5,8,11]. Thus, multi-modality efforts at history taking, imaging techniques, histopathological diagnosis (to rule out malignancy), and serological tests are crucial for the diagnosis of secondary syphilis with atypical presentation.

Standard treatment for syphilis is penicillin [1]. Benzylpenicillin (also known as penicillin G) or benzathine benzylpenicillin is administered via intramuscular injection. For neurosyphilis including ocular involvement, a higher dose of penicillin is administered intravenously [1,6]. Alternative therapies include doxycycline and ceftriaxone. It should be noted that fluoroquinolone, sulphonamide, and aminoglycoside antibiotics are not effective [1]. In Japan, intramuscular injection of penicillin is not approved, since fatal cases were reported following the procedure. Alternatively, oral amoxicillin is recommended. In the present case, oral amoxicillin treatment for two weeks was effective as reflected by a decrease in RPR from 67.3 RU to 7.9 RU and resolution of other symptoms, but it was not sufficient for treatment of the periportal lymph node.

Conclusions

Tonsillitis, cervical lymphadenopathy, lung lesions, and elevated liver enzymes can be manifestations of secondary syphilis. Clinicians should consider syphilis in the differential diagnosis of tonsillitis with cervical lymphadenopathy. Detailed inquiries on sexual activities and serological tests are crucial for diagnosis.

Conflict of interest

None.

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