

CASES

Necrotic pulmonary nodules in secondary syphilis

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A 56-year-old woman presented to the emergency department with worsening left-sided pleuritic chest pain, rash and painful eyes. Her symptoms had started about four weeks earlier with gradual left-sided chest pain. She had presented to the emergency department at that time, but after a negative chest radiograph, she had been sent home with a provisional diagnosis of pleuritis and instructions to follow up with her family physician if symptoms worsened or did not resolve.

At the current visit, the woman reported a one-week history of malaise and weight loss of 2.5 kg over three weeks. She also noted a three-week history of tenderness of her scalp and a nonpruritic, nontender rash on her forehead that extended to her trunk, palms and soles. She said that her eyes had suddenly become red and painful two weeks before presentation. An ophthalmologist had diagnosed episcleritis, with no retinal or vitreal pathology.

Aside from a history of hyperlipidemia, the patient had been previously healthy and had no history of immunosuppression. Her medications had not been changed recently and included atorvastatin (10 mg/d), acetylsalicylic acid (81 mg/d), and vitamin D and calcium supplements. She was sexually active with one male partner, who had previously been treated for sexually transmitted infections.

On physical examination, the patient was afebrile and appeared comfortable, with no respiratory distress. She had a macular rash predominantly on her trunk and soles of her feet (Figure 1), with occasional scattered lesions on her palms. She had no oral or genital lesions. Findings from cardiovascular, respiratory and abdominal examinations were normal.

A chest radiograph showed a 1.5-cm rounded opacity in the left middle to lower lobe of her lung that had not been present four weeks earlier. Computed tomography revealed four necrotic-appearing nodules in the right middle lobe and both lower lobes of the lungs that measured 6–29 mm in diameter (Figure 2). Results of laboratory investigations are shown in Table 1. The lev-

els of electrolytes, creatinine, calcium and albumin and the results of urinalysis were within normal limits. Results of serologic testing indicated immunity to hepatitis A and B, and they were negative for hepatitis C, HIV and mononucleosis.

Serologic testing for syphilis was ordered because of the characteristic rash involving the patient's palms and soles. Enzyme immunoassay was positive for antibodies to *Treponema pallidum*, the rapid plasma reagin test was reactive with a titre of 1:128, and the *T. pallidum* particle agglutination assay was reactive. Skin biopsy, performed before our assessment, showed perivascular and interstitial mixed infiltrate of plasma cells with focal collections of histiocytes and giant cells. No organisms were seen on microscopy with Ziehl–Neelsen staining; dark-field microscopy was not performed. Warthin–Starry silver staining failed to show any spirochetes, but polymerase chain reaction testing was positive for syphilis with the use of three common treponemal gene targets (bmp, tpp-47 and polA). The patient was unable to produce sputum for analysis.

Based on the clinical presentation and the serologic results, we started empirical treatment of secondary syphilis, rather than delay treatment until a bronchoscopy could be performed. Benzathine penicillin (2.4 million units intramuscularly) was given weekly for three weeks, and the patient was monitored for response. The patient's fatigue, malaise, rash and chest pain resolved within two weeks after the start of treatment. After treatment, her vision became more blurry and sensitivity to light in her right eye increased. An ophthalmologist subsequently diagnosed uveitis and prescribed prednisolone eye drops. No retinal or vitreal involvement had developed.

KEY POINTS

- Although the incidence of primary and secondary syphilis is increasing in Canada, pulmonary involvement in secondary syphilis is uncommon.
- Clinical manifestations of pulmonary involvement in secondary syphilis vary, with some patients having no or mild symptoms.
- Imaging in pulmonary syphilis most commonly reveals pulmonary nodules.

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Three months after treatment, computed tomography of the chest showed almost complete resolution of the pulmonary nodules (Figure 3). The rapid plasma reagin titre at three months decreased to 1:4 and further decreased to 1:1 at one year after treatment.

Discussion

The rate of primary and secondary syphilis in Canada increased by 500% between 1998 and 2007, from 177 cases reported in 1999 to 1206 in

2007.¹ Similar increases have been observed in the United States, with the rate of primary and secondary syphilis increasing annually between 2001 and 2008 among both men and women.² In the United States, 46 277 cases of syphilis (all stages) were reported to the US Centers for Disease Control and Prevention in 2008. Of these, 29.1% were primary or secondary syphilis, 26.8% were early latent syphilis, 43.1% were in the late latent stage, and 1% represented congenital syphilis.²

Typically, syphilis first appears as a primary chancre after an incubation period of two to six weeks on average. The chancre is usually a painless smooth papule. It then erodes, becoming indurated with raised and firm borders that have a characteristic cartilaginous consistency. In men, the chancre is often located on the penis; in those who practise receptive anal sex, the chancre may be found in the anal canal. In women, the chancre may occur on the cervix or labia. In men or women who practise oral sex, the chancre can develop in the mouth.

This primary stage is followed by the mucocutaneous signs and generalized symptoms of the secondary stage, which usually appear six to eight weeks after the chancre heals. Typical mucocutaneous signs include pale red or pink, nonpruritic macular, maculopapular, papular or pustular discrete lesions (3–10 mm in diameter) on the trunk and proximal extremities. These lesions often appear on the palms and soles. Generalized symptoms include malaise, weight loss, pharyngitis, low-grade fever, anorexia, arthralgias and headache. Generalized painless lymphadenopathy may also occur.



Figure 1: Lesions on the soles of the feet of a 56-year-old woman with secondary syphilis.

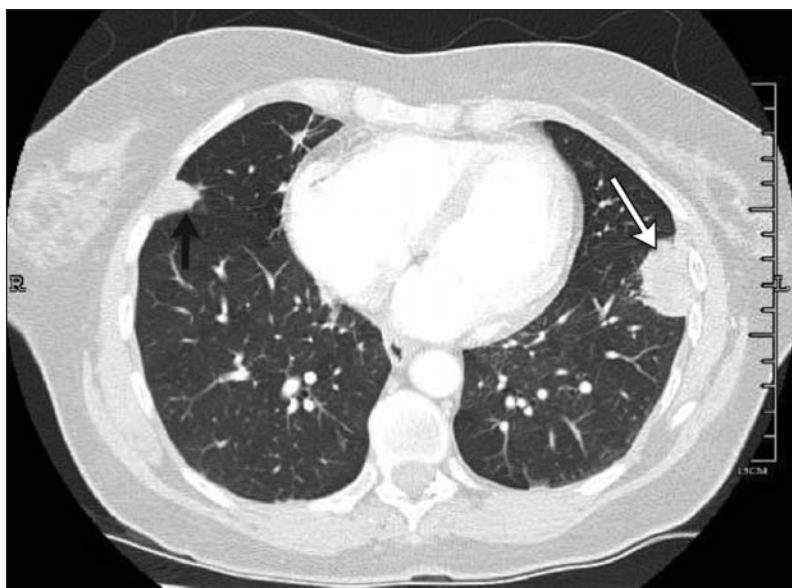


Figure 2: Computed tomography scan showing nodules in the left lower lobe (white arrow) and right lower lobe (black arrow) of the patient's lungs.

Table 1: Results of laboratory investigations

Test (normal values)	Result
Hemoglobin level, g/L (120–160)	111
Leukocyte count, $\times 10^9/L$ (4.5–11.0)	6.9
Platelet count, $\times 10^9/L$ (130–400)	525
Aspartate aminotransferase level, U/L (5–34)	21
Alanine aminotransferase level, U/L (7–40)	26
Alkaline phosphatase level, U/L (35–104)	145
Erythrocyte sedimentation rate, mm/h (1–20)	45
C-reactive protein level, mg/L (< 10)	57.7
Rheumatoid factor, kIU/L (< 20)	54
Antinuclear antibody	Negative
Blood culture for bacteria	Negative
HIV type 1 and 2 antibodies	Nonreactive

Secondary lesions resolve within two to six weeks and are followed by the clinically silent latent stage, detected only by means of serologic testing. If untreated, the condition will progress to tertiary syphilis in about one-third of patients.³

Pulmonary syphilis

Pulmonary syphilis is uncommon. We were able to identify only 11 case reports published since 1967 (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.091479/DC1). Before 1967, lung involvement in syphilis was thought to be a complication of either tertiary or congenital syphilis.⁴⁻⁶ Most cases of tertiary syphilis in the literature were definitively diagnosed by pathological findings of tracheobronchial syphilis, luetic pneumonia or typical gummata (syphilitic granulomas), and the absence of acid-fast bacilli on autopsy or following lobectomy or pneumonectomy.^{4,5,7}

The clinical presentation of pulmonary syphilis varies and includes cough, hemoptysis, dyspnea and chest pain. Some patients have no respiratory symptoms.⁵ Tracheobronchial syphilis affects limited sections of the airways; if it is severe, subsequent healing and fibrosis can lead to distortion of bronchus and adjacent lung.⁴

Luetic pneumonia is chronic and involves both the airspace and interstitium. The disease tends to attack the middle and lower lobes of the lungs.⁵ Microscopically, a heavy inflammatory infiltrate of histiocytes, plasma cells and lymphocytes may be seen, as well as small foci of necrosis.⁴

Typical gummata have a centre of pale grey or yellow dry necrosis encased by a fibrous capsule from which irregular strands of fibrotic lung extend into and distort the surrounding tissue.^{4,5}

Box 1: Criteria for the clinical diagnosis of pulmonary involvement in secondary syphilis⁸

- History and physical findings typical of secondary syphilis*
- Serologic test results positive for syphilis
- Pulmonary abnormalities seen on radiographs with or without associated pulmonary symptoms or signs
- Exclusion of other forms of pulmonary disease when possible by findings of serologic tests, sputum smears and cultures, and cytologic examination of sputum
- Therapeutic response to antisyphilitic treatment visible on radiographs

*The manifestations of secondary (or disseminated) syphilis are varied but are typically characterized by nonpruritic rash, constitutional symptoms and, less commonly, involvement of the central nervous system, glomerulonephritis, nephrotic syndrome, hepatitis, intestinal wall invasion or arthritis.³

These gummata can cause necrosis of the alveolar wall and destruction of elastic tissue, erode into adjacent bronchi and lead to cavitation.^{4,5}

Diagnosis of pulmonary syphilis

The signs and symptoms of secondary syphilis with pulmonary nodules described in our patient meet the diagnostic criteria proposed by Coleman and colleagues⁸ (Box 1). These criteria were developed in 1983 to standardize the diagnosis of pulmonary involvement in secondary syphilis.⁸ With the emergence of HIV infection, and an increasing incidence of syphilis, a corresponding increase in pulmonary cases was anticipated. The criteria were developed by expert consensus by reviewing suggested criteria for the diagnosis of pulmonary disease in tertiary syphilis and case reports of pulmonary involvement in secondary syphilis.⁸

Although the differential diagnosis of infectious pulmonary nodules is extensive, in our patient it was limited to infections that would completely resolve following a short course of penicillin monotherapy. This excludes mycobacterium, endemic fungi, and *Aspergillus* and *Nocardia* species. Among bacterial causes sensitive to penicillin, aspiration pneumonia, *Pasteurella multocida*, actinomycosis and streptococcal septic emboli could cause this radiographic picture. In our patient, there was no supporting history for an aspiration event or exposure to animals, and actinomycosis or septic emboli would likely not have been treated successfully with the short course of penicillin given.

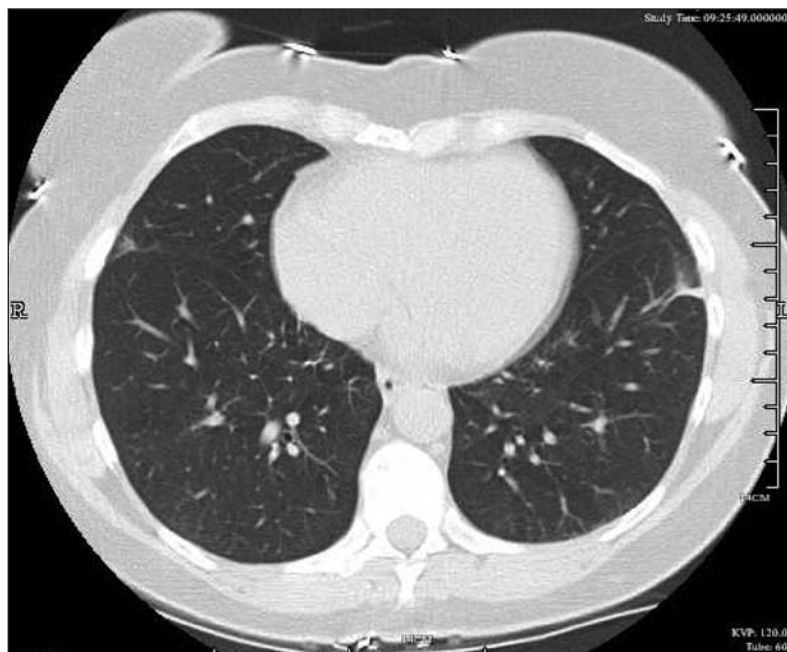


Figure 3: Computed tomography scan three months after treatment with penicillin, showing resolution of the pulmonary nodules.

Our patient had necrotic bi-basilar pulmonary nodules in secondary syphilis. Because necrosis is a pathological finding seen in both luetic pneumonia and gummata in tertiary syphilis, our patient's necrotic nodules may have been precursors to typical gummata. The histology of gummata identified in other organs often shows granulomatous inflammation with a central area of necrosis due to endarteritis obliterans.³ This process may have occurred in our patient, causing her pulmonary nodules to necrotize.

Given that patients may be asymptomatic or have mild respiratory symptoms, pulmonary involvement in secondary syphilis may be under-recognized because chest imaging is not routinely performed. However, previous studies, now historical, failed to support this hypothesis. In a study between 1939 and 1944 at Bellevue Hospital involving 1500 patients with secondary syphilis, none of the patients had radiologic evidence of pulmonary involvement.⁹ In addition, autopsy studies from the early 1900s identified few cases of pulmonary involvement in secondary syphilis.¹⁰ Whether these findings would be replicated with the increased resolution of modern diagnostics remains an open question.

Impact of HIV co-infection

Most reports of pulmonary syphilis predate the emergence of HIV. An interaction between HIV and syphilis may change the presentation of secondary syphilis.¹¹ The suppression of the immune system seen in patients who are HIV positive may allow syphilis to present atypically. A higher proportion of patients with HIV infection than without have asymptomatic primary syphilis; therefore, more patients who are HIV positive may present with secondary disease.¹¹ Also, because early neurologic involvement in syphilis is more common in patients who are HIV positive, syphilis infection in this group may be more aggressive.¹¹

Most cases of syphilis in developed countries occur in men who have sex with men. Our report, however, describes heterosexual transmission, part of an increasing trend in recent years.^{1,2} With the increasing prevalence of syphilis and its changing demographic profile,

clinicians need to consider syphilis in the differential diagnosis of patients presenting with pulmonary symptoms and cutaneous lesions.

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Clinical resources

- Public Health Agency of Canada: Syphilis facts and FAQs (www.phac-aspc.gc.ca/std-mts/syph_faq-eng.php)
- Public Health Agency of Canada: Guidelines on sexually transmitted infections (www.phac-aspc.gc.ca/std-mts/sti-its/pdf/510syphilis-eng.pdf)
- US Centers for Disease Control and Prevention: Syphilis fact sheet (www.cdc.gov/std/Syphilis/STDFact-Syphilis.htm)