Secondary Pulmonary Syphilis: Report of A Likely Case and Literature Review

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We report the case of a homosexual, HIV-positive man with typical secondary syphilis and multiple excavated pulmonary subpleural nodules. Syphilis with direct pulmonary involvement was suggested by a positive result of PCR of a bronchoalveolar lavage fluid specimen, then confirmed by a positive therapeutic test result. Only 9 reports of pulmonary involvement in secondary syphilis have been reported to date in the English-language literature. Clinicians should be aware of this atypical localization of syphilis.

The incidence of primary and secondary syphilis has increased substantially during the past years in populations engaged in high-risk behavior [1]. Syphilis with pulmonary involvement (hereafter referred to as pulmonary syphilis) was limited to congenital and tertiary syphilis during the preantibiotic era but has been described as occurring mostly during secondary syphilis since 1967. We report a case with unusual radiological features that was diagnosed with a recently developed PCR method. English-language literature is reviewed, and pulmonary secondary syphilis is described.

Case report. A 34-year-old, HIV-positive, homosexual man was admitted to the hospital with a 2-month history of progressive weakening, anorexia, 6-kg weight loss, and night sweats. The patient also complained of anterior, right-side chest pain. He was not receiving antiretroviral therapy, and his CD4+ lymphocyte count was 380 cells/mm³. His sexual partner had presented with an untreated ulceration of the penis 3 months previously.

Physical examination showed a generalized maculopapular rash with 3-mm thick, peripheral desquamation on his right palm. His body temperature was 38.5°C. Heart and lung examination findings were normal. Palpation of the right hypochondrium was painful. A careful mouth and throat examination showed no mucosal lesion. There was no anogenital lesion.

Chest x-ray films showed a right subhilar nodular opacity. The chest CT scan revealed several bilateral, round, excavated opacities measuring from 20–40 mm in diameter (figure 1) and 1 subtracheal adenopathy. The alkaline phosphatase level was 149 U/L (normal range, <110 U/L), the γ-glutamyl transpeptidase level was 92 U/L (normal range, <65 U/L), and the β₂-microglobulin level was 3.2 mg/L (normal range, <2 mg/L). Results of the hemogram, other serum chemistry tests, and urinalysis were normal. The results of tests for antineutrophil cytoplasmic antibodies and rheumatoid factor were negative. Both the Venereal Disease Research Laboratory (VDRL) test (titer, 1:16) and the fluorescent treponemal antibody–absorbed test (titer, 1:800) were positive.

Because the patient refused biopsy, bronchoalveolar lavage in the medial lobe was performed. Cytological examination of a lavage fluid specimen showed a predominance of macrophages (94%). Quantitative bacterial culture had negative results. Pathogen-specific tests were negative for Mycoplasma species, Nocardia species, Rhodococcus equi, mycobacteria, fungi, Pneumocystis species, and pneumotropic viruses (influenza viruses A and B, parainfluenza virus 1, 2 and 3, and respiratory syncytial virus [by immunofluorescence and cell culture]; herpes viruses, varicella-zoster virus, cytomegalovirus, and Epstein-Barr virus [by PCR and cell culture]; and adenovirus and enteroviruses [by cell culture]). The result of PCR that targeted the DNA polymerase I of Treponema pallidum (polA) [2] was positive, and its validity was supported by the results of direct sequencing. CSF was normal (no leukocytes, a negative VDRL result, and a negative polA PCR result). Blood culture results remained negative. Transthoracic echocardiography and jugular ultrasonography findings were normal.

Intravenous penicillin G (18 megaunits per day for 14 days) was the only medication administered, except for tramadol. On the first night in the hospital, the patient complained of nausea, and fever with a temperature of 38.6°C was observed. Chest pain disappeared after 3 days. Finally, a radiography-guided transparietal biopsy was performed on hospital day 12. Results of standard bacteriological, mycobacterial, and mycological tests were negative, as were the results of polA PCR. Histopathological examination showed small histiocytic and lymphoplasmocytic granulomas within organized pneumonia. Silver stain-
Figure 1. Thoracic CT scan showing 2 bilateral, excavated, pulmonary, subpleural, nodular opacities

ing did not reveal any spirochetes, and a diagnosis of lymphoma was excluded after immunohistochemical testing.

The patient was discharged on hospital day 15. Follow-up examinations showed a normalization of his clinical status. After 3 months, CT showed progressive disappearance of the pulmonary nodules, and serologic testing for syphilis showed a drop in VDRL titer to 1:1.

**Literature review.** We searched the Medline database with the keywords “syphilis,” “Treponema pallidum,” “secondary,” “early,” “pulmonary,” and “lung” to identify case reports published in English-language literature from January 1966 to May 2005. Five reports that recorded observations with either no skin eruption or no history of sexual contact in the months before hospitalization were excluded.

**Results.** Nine cases of pulmonary involvement in secondary syphilis have been reported since 1966 (table 1). Patients were HIV-positive in 2 cases. The diagnosis of secondary syphilis was confirmed by high values for nontreponemal tests, as well as, in 4 cases, direct demonstration of *T. pallidum* organisms (in a skin biopsy specimen, in 2 cases; in a rectal biopsy specimen, in 1 case; and by pleural cytological examination, in 1 case). Chest pain was present in 5 patients, and lung involvement was revealed by chest x-ray in the 4 others. Radiological presentation was nonspecific; reports described nodular opacities (solitary in 4 cases and multiple in 2) or infiltrates (in 3 cases), occasionally associated with pleural effusion (2 cases). Among the 4 cases for which bronchopulmonary samples were obtained, direct evidence of *T. pallidum* was not present in 3 and was present in 1 (spirochetes were visualized in pleural fluid with May-Grünwald-Giemsa stain). Histological examination revealed nonspecific granuloma in the 2 patients who underwent biopsies. After specific treatment, pulmonary symptoms resolved faster than did mucocutaneous signs, and radiological normalization took from 2 weeks to 4 months.

**Discussion.** Secondary pulmonary syphilis is very rare; in a study conducted between 1939 and 1944 with 1500 patients who had secondary syphilis, no patient showed radiographic evidence of pulmonary involvement (S. Landry, quoted in Biro et al. [3]). However, pulmonary syphilis was first described in the 1880s. In the preantibiotic era, the prevalence of lung involvement in persons known to have had syphilis and who underwent autopsy varied from 1% to 12.5% [5]. Descriptions of pulmonary syphilis at that time were mainly of congenital and tertiary syphilis with nodular (gummatous) or fibrotic lesions. However, since 1967, there have been reports of 9 unquestionable cases of secondary pulmonary syphilis.

Radiological examination plays a major role in the diagnosis of pulmonary syphilis. Pulmonary lesions can appear as bilat-
Table 1. Comparison of cases of secondary syphilis with pulmonary involvement in the English-language literature.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Age in years, sex</th>
<th>HIV infection status</th>
<th>Pulmonary symptoms and/or physical findings</th>
<th>Thoracic radiological findings</th>
<th>Method of obtaining bronchopulmonary samples and/or test results</th>
<th>Extrapulmonary physical and/or biological findings</th>
<th>Nontreponemal serological test performed (titer)</th>
<th>Drug therapy</th>
<th>Outcome; time to radiological normalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>1967</td>
<td>52, M</td>
<td>Unknown</td>
<td>None</td>
<td>Multiple bibasilar ill-defined nodules</td>
<td>None</td>
<td>Rash, alopecia, sore throat, and uveitis</td>
<td>VDRL (1:1024)</td>
<td>Penicillin G, 0.6 MU/day im for 13 days</td>
<td>Cured; 4 months</td>
</tr>
<tr>
<td>[4]</td>
<td>1979</td>
<td>31, M</td>
<td>Unknown</td>
<td>Dorsal pain and crepitating rales of the left base of the lung</td>
<td>LLL solitary round opacity (diameter, 4–5 cm), pleural effusion&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Bronchial washing; negative darkfield microscopy finding</td>
<td>Rash, cholestasis, and fever</td>
<td>VDRL (1:8)</td>
<td>Penicillin G, 1 MU/day iv for 10 days; then benzathine penicillin, 2.4 MU/week im for 3 weeks</td>
<td>Cured; unknown</td>
</tr>
<tr>
<td>[5]</td>
<td>1980</td>
<td>39, M</td>
<td>Unknown&lt;sup&gt;a&lt;/sup&gt;</td>
<td>None</td>
<td>Lingular and RLL infiltrates</td>
<td>None</td>
<td>Rash</td>
<td>VDRL (1:512)</td>
<td>Benzathine penicillin, 2.4 MU im</td>
<td>Cured; 4 months</td>
</tr>
<tr>
<td>[6]</td>
<td>1983</td>
<td>37, M</td>
<td>Unknown&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Dorsal pain</td>
<td>LLL ill-defined nodule&lt;sup&gt;d&lt;/sup&gt;</td>
<td>None</td>
<td>Rash, mucus patch on the tongue, and fever</td>
<td>VDRL (1:1024)</td>
<td>Tetracycline, 2 g/day po for 15 days&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Cured; 1 month</td>
</tr>
<tr>
<td>[7]</td>
<td>1985</td>
<td>48, M</td>
<td>Unknown</td>
<td>Chest pain</td>
<td>LLL solitary opacity</td>
<td>Bronchial washing, negative darkfield microscopy finding; transbronchial biopsy, granuloma and multinuclear cells</td>
<td>Rash, lesions of the soft palate, penile ulcer, and cholestasis</td>
<td>VDRL (1:32)</td>
<td>Amoxicillin po for 2 weeks then benzathine penicillin 1.2 MU/day im for 28 days</td>
<td>Cured; 3 months</td>
</tr>
<tr>
<td>[8]</td>
<td>1989</td>
<td>33, M</td>
<td>Unknown</td>
<td>None</td>
<td>RUL solitary nodule (diam, 2–3 cm)</td>
<td>None</td>
<td>Rash, rectal mass, and hepatitis</td>
<td>RPR (1:128)</td>
<td>Benzathine penicillin 2.4 MU/week im for 2 weeks</td>
<td>Cured; 1.5 months</td>
</tr>
<tr>
<td>[9]</td>
<td>1990</td>
<td>37, M</td>
<td>Positive</td>
<td>None</td>
<td>Bifasilar reticular infiltrates</td>
<td>Bronchial biopsy, foci of epithelioid granuloma with negative Wharthin-Starry silver stain result</td>
<td>Rash, penile ulcer, and hepatitis</td>
<td>RPR (1:512)</td>
<td>Penicillin G, iv; “a course of neurosyphilis completed” (p. 629)</td>
<td>Cured; 1 month</td>
</tr>
<tr>
<td>[10]</td>
<td>1996</td>
<td>68, M</td>
<td>Positive</td>
<td>Unknown</td>
<td>LLL pneumonia with pleuritis</td>
<td>Pleural puncture; characteristic cytomorphometry and spirochetes found with MGG and Steiner stains</td>
<td>Rash</td>
<td>RPR (&gt;1:1024)</td>
<td>Benzathine penicillin, 2.4 MU/week im for 3 weeks, along with imipenem and cilastatin</td>
<td>Cured; 2 weeks</td>
</tr>
<tr>
<td>[11]</td>
<td>2003</td>
<td>50, M</td>
<td>Negative</td>
<td>Intermittent cough and inspiratory crackles of the right base of the lung</td>
<td>Multiple bibasilar ill-defined nodules&lt;sup&gt;d&lt;/sup&gt;</td>
<td>None</td>
<td>Rash, conjunctivitis, nephropathy, meningitis, cholestasis, and fever</td>
<td>RPR (&gt;1:266)</td>
<td>Penicillin G, iv&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Cured; 2 months</td>
</tr>
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**NOTE.** im, intramuscularly; iv, intravenously; LLL, left lower lobe; MGG, May-Grünwald-Giemsa; MU, megaunit; po, orally; RLL, right lower lobe; RPR, rapid plasma reagin; RUL, right upper lobe; VDRL, Venereal Disease Research Laboratory test.

<sup>a</sup> Multiple anonymous homosexual contacts in San Francisco in 1980.

<sup>b</sup> Homosexual man from North Carolina who had >100 sexual partners in the past year in 1983.

<sup>c</sup> This patient had an allergy to penicillin.

<sup>d</sup> CT performed.

<sup>e</sup> For neurological involvement.
eral infiltrates, solitary or multiple subpleural nodules, pleural effusion, or lymphadenopathy. No specific lesion can be identified, even with CT. The case we describe is the first with excavated nodules.

The difficulty is to assert that a case of pneumonia is caused by syphilis. Our observations met all the clinical criteria proposed by Coleman et al. [5] for defining secondary pulmonary syphilis: (1) historical and physical findings typical of secondary syphilis; (2) serologic test results positive for syphilis; (3) pulmonary abnormalities seen radiographically with or without associated symptoms or signs; (4) exclusion of other forms of pulmonary disease, when possible, according to findings of serological tests, sputum smears and cultures, and cytological examination of sputum; and (5) response to antisyphilis therapy of signs found by radiological examination. The unusual radiological aspect—especially in the context of HIV infection—required a more aggressive diagnostic strategy; the findings of bronchoalveolar lavage and lung biopsy excluded specific infections (infection due to Rhodococcus equi, Nocardia species, Aspergillus species, Mycobacterium species, and pneumotropic viruses) and tumor disease (lymphoma, Kaposi sarcoma, and carcinoma metastases). Mycotic or bacterial metastases, systemic diseases (such as Wegener granulomatosis, rhumatoid polyarthritis, and sarcoidosis), and vasculopathy (such as Rendu-Osler-Weber syndrome and lung infarction) were excluded biologically and radiologically.

However, in view of the many differential diagnoses for pulmonary disease and the length of time until therapeutic response (up to 4 months), direct evidence of T. pallidum in the lung might prove helpful in conservative initial management. Direct examination by darkfield microscopy or silver stain has proved too insensitive; these methods showed rare spirochetes in the pleural fluid of only 1 patient. Specific immunostaining would be more sensitive. Our study is the first to use PCR to show direct pulmonary involvement in syphilis. PCR with the enzyme poIA has been shown to be both sensitive, with a detection level of 10 T. pallidum organisms per 5-μL sample, and specific, with use of strands specific to T. pallidum [2]. PCR has been used to characterize the syphilitic nature of other unusual localizations of infection, such as in the cerebral, gastric, or testicular regions [12–14]. However, during bacteremic secondary syphilis, the results of PCR for many tissue samples, including samples of oral lesions [15] and blood [16], have been positive, which indicates that positive PCR results for bronchoalveolar lavage fluid specimens could be the possible result of contamination by pharyngeal or blood samples.

The following factors led us to propose transparietal pulmonary biopsy: easy access to the nodules, their failure to regress after 12 days of intensive therapy with penicillin, and the possibility of coexisting diseases during secondary syphilis [17]. The biopsy revealed poorly differentiated granuloma. Granuloma, though not specific to the disease, appears evocative of pulmonary secondary syphilis [7, 9]. The typical obliterative endarteritis with perivasculat plasma cell infiltrate has never been described in the small nonsurgical biopsies performed during pulmonary secondary syphilis [7, 9]. Even epithelioid cell granulomas occur occasionally in secondary syphilis, especially in the late stage [7]. In our case, the radiological presentation—multiple, subpleural, excavated, well-defined nodules—was very similar to previous descriptions of pulmonary gumma [18], but histological examination did not confirm this impression. However, the biopsy specimen was small, and the biopsy was performed on a nodule that was not excavated. The necrotizing, granulomatous lesions biopsied may have represented forerunners of gummas.

This is probably the fifth description of secondary pulmonary syphilis in an HIV-infected patient, as 2 of the previously reported cases involving patients with pneumonitis [5, 6] occurred in homosexual men treated during the AIDS era. The common mode of transmission explains the frequent association of HIV and syphilis infections. Because intact cell-mediated immune response is probably critical for the control of T. pallidum infection, subtle functional T cell deficits, which are seen even in early HIV infection, may have allowed for the evolution of the atypical pulmonary presentation reported here. However, secondary forms do not seem more severe in HIV-positive patients than they are in HIV-negative patients [19], even if there is an increased rate of early ophthalmic and neurological involvement [20]. Pulmonary syphilis often appears to be associated with various other extracutaneous localizations of infection and, especially frequently, with hepatic involvement.

The strong diagnostic value of clinical and radiological response to penicillin therapy relies on its narrow spectrum. In contrast to the clinical evolution, the time to radiological normalization is long, especially in the instance of follow-up with the very sensitive CT. Today, new diagnostic tools, such as T. pallidum–specific PCR, can be used in unusual localizations of this usually protean illness, even if the response to penicillin remains the best confirmation of pulmonary secondary syphilis.

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References