Streptomyces Pneumonia in a Patient with Human Immunodeficiency Virus Infection: Case Report and Review of the Literature on Invasive Streptomyces Infections

Eileen F. Dunne, William J. Burman, and Michael L. Wilson

Streptomyces species are most widely known for their production of antimicrobial substances and, apart from mycetoma, have rarely been reported as a cause of infection. We describe a patient with early human immunodeficiency virus infection who presented with fever, cough, and nodular pulmonary infiltrates. Open lung biopsy revealed necrotic tissue and a sulfur granule; aerobic bacterial cultures yielded Streptomyces species. The patient was treated successfully with clarithromycin for 6 months. We review the clinical presentation and treatment of invasive streptomyces infections.

Members of the genus Streptomyces are aerobic actinomycetes known for the production of antibiotics used to treat bacterial, mycobacterial, fungal, and parasitic infections. Streptomyces species can also cause human disease. Mycetoma, a chronic suppurrative infection of the skin and underlying soft tissue, is the most common presentation of streptomyces infection; visceral infections with these organisms appear to be rare. We report a case of pneumonia caused by Streptomyces species in a patient with HIV infection, and we review the literature on invasive streptomyces infections.

Case Report

A 43-year-old male presented with complaints of progressive weight loss over 2 months, night sweats and fatigue of 2 weeks’ duration, a nonproductive cough, dyspnea, and pleuritic chest pain. HIV infection had been diagnosed 8 years previously; his most recent CD4 cell count was 800/mm³. Notable findings of the initial physical examination included a temperature of 38.9°C, diffuse inspiratory crackles, and a right-sided pleural friction rub. The patient had no evidence of dental abnormalities. Laboratory tests revealed a WBC count of 15,800 cells/mm³ and modest increases in levels of alkaline phosphatase, lactate dehydrogenase, and hepatic transaminases. A chest radiograph (figure 1A) showed multiple, 0.5–3.0-cm, nodular opacities in both lung fields; a CT scan of the chest did not show any cavitation within these lesions or any intrathoracic lymphadenopathy (figure 1B). An initial sputum culture yielded normal oral flora.

Therapy with ceftriaxone and prophylactic doses of trimethoprim-sulfamethoxazole (TMP-SMZ) was started while awaiting further diagnostic studies. An open lung biopsy revealed acute and organizing pneumonia with focal necrosis and a sulfur granule (figure 2). Within the sulfur granule there was evidence of branching organisms with a beaded appearance on gram staining. Aerobic culture of the tissue biopsy specimen on blood agar yielded a beaded gram-positive bacterium that did not stain partially acid fast. All anaerobic, fungal, and mycobacterial cultures of the operative specimen were negative. This organism was identified as Streptomyces on the basis of morphology; negative partial acid-fast staining; sensitivity to lysozyme; and hydrolysis of xanthine, tyrosine, and casein [1]. The organism was confirmed to be a Streptomyces species at the Centers for Disease Control and Prevention (CDC) on the basis of cell-wall studies that demonstrated the presence of L-diaminopimelic acid [1, 2]. A susceptibility panel performed with use of the broth microdilution technique at the CDC showed that the isolate was susceptible to TMP-SMZ (MIC, <0.06/1.19 μg/mL), imipenem (MIC = 0.25 μg/mL), ceftriaxone (MIC, <1.0 μg/mL), and clarithromycin (MIC, <0.13 μg/mL) [3].

The patient’s condition improved clinically after treatment with ceftriaxone, which was switched to that with oral TMP-SMZ (double-strength t.i.d.). He subsequently developed fevers and a rash, necessitating discontinuation of TMP-SMZ. He was then treated with clarithromycin (500 mg b.i.d.) on the basis of the in vitro susceptibility data as well as intolerance of TMP-SMZ, and his symptoms abated within 1 month. The nodular infiltrates resolved after 3 months. Treatment with clarithromycin was discontinued after 6 months, and no signs of relapse have been observed in follow-up evaluations performed over 8 months.

Discussion and Review of the Literature

The aerobic actinomycetes, including Streptomyces and Nocardia species, are bacteria that belong in the order Actino-
mycetales. At one time these microorganisms were classified as fungi because they possess true aerial hyphae, but they are now recognized as bacteria. Most actinomycetes are gram-positive, filamentous, partially acid-fast, branched bacteria. Species of the genus *Streptomyces* are characterized by formation of extensive, branched aerial hyphae with long chains of conidia and the cell-wall peptidoglycan L-diaminopimelic acid [1, 2]. The natural habitat of most *Streptomyces* species is the soil, where they are found on surfaces that support their mycelial growth [4]. More than 3,100 *Streptomyces* species have been described [5]. Initially, identification to the species level was based on subjectively chosen morphological features. Recently, morphological characteristics have given way to more objective classification methods such as rapid enzyme tests of fluorophores [5, 6]. Currently, the species taxonomy is changing rapidly as new techniques allow more specific differentiation.

The clinical significance of recovering this organism is often unclear because there have been many reports of isolation of *Streptomyces* species without definitive evidence of its pathogenic role. *S. violaceoruber*, *S. coelicolor*, and *S. albus* have been isolated from dental caries, blood, tonsils, skin, and sputum [4]. *S. candidus* has been isolated from the purulent exudate of a fractured patella, *S. horton* from pus, and *S. willmorei* from a liver abscess [4]. In addition, *S. gedaensis* has been recovered from sputum and abscesses [4]. However, none of these reports described the *Streptomyces* species as the principal pathogen. Therefore, the role of *Streptomyces* species in visceral infections has been controversial in the setting of mixed infections in which other probable primary pathogens have also been isolated.

The present case was unusual, as only three other cases of streptomyces pneumonia have been described [7–9]. It clearly illustrates the potential of *Streptomyces* species to cause invasive infection. *Streptomyces* was determined to be the primary pathogen because the histopathological finding of a sulfur granule was compatible with the presence of this organism, other pathogens were excluded by culture, and *Streptomyces* species were isolated in pure culture of the tissue specimens. In addition, the response to therapy was dramatic, although the therapy was active against organisms other than *Streptomyces* species.

Histopathologic examination of the lung biopsy specimen revealed a sulfur granule, a finding typical of visceral actinomycoses infection and visceral botryomycosis caused by bacteria such as *Staphylococcus aureus* and species of *Pseudomonas* or *Proteus*. In contrast, *Nocardia* species have been reported to cause sulfur granules in mycetomas but not in visceral infections [10]. Thus, we may add *Streptomyces* species to the list of potential pathogens causing sulfur granules in visceral infection.
To identify all reports of invasive disease due to *Streptomyces* species, we performed a MEDLINE search of the worldwide literature through January 1997 and reviewed the references from previous papers on *Streptomyces*. Mycetomas are the most common clinical presentation of streptomyces infection, and *S. somaliensis* has been identified as one of the principal etiologic agents of actinomyctoma in South America, Africa, India, Mexico, Malaysia, and the United States [11, 12]. The clinical presentation, microbiology, and treatment of mycetoma have been reviewed previously; thus, we did not include this manifestation of streptomyces infection in our review. We defined invasive disease as infection other than superficial skin infections or mycetoma.

There have been only a few reports of *Streptomyces* species causing infection other than mycetoma (table 1). *Streptomyces* species have been described as the cause of septicemia and primary lung involvement [7]; *Streptomyces* was cultured in a case of chronic pericarditis in which extensive disease was observed in histopathologic specimens [13]; a brain abscess has been attributed to *S. griseus* [14]; an abdominal abscess with peritonitis was caused by *S. somaliensis* [15]; and a case of endocarditis has been attributed to *Streptomyces* species [16]. In the majority of these cases, the outcome was good, with resolution of the infection. Treatment included many different antimicrobials, some with in vitro activity against *Streptomyces* species.

Infections caused by aerobic actinomycetes in patients with HIV disease have been attributed predominantly to *Nocardia* and *Rhodococcus* species. There have been only three case reports of streptomyces infection in HIV-infected patients. A report by Caron and colleagues [8] described a man with advanced HIV infection and nodular infiltrates on a chest radiograph. *Streptomyces* species grew in culture of a bronchoscopic specimen [8]. Ahmed and colleagues [9] described a case of streptomyces pneumonia and monoarthritis in a patient with advanced HIV disease. A case of lymphadenitis was attributed to *Streptomyces* species in an HIV-infected patient; however, *Mycobacterium tuberculosis* also grew in culture [17]. It is of interest that rhodococcus and nocardia infections in HIV-positive patients can present as nodular infiltrates, similar to the

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Reference</th>
<th>Etiologic organism</th>
<th>Presentation</th>
<th>Culture</th>
<th>Underlying condition</th>
<th>Treatment</th>
<th>Duration of treatment (mo)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[PR]</td>
<td><em>Streptomyces</em></td>
<td>Pneumonia</td>
<td>Lung biopsy specimen</td>
<td>HIV infection*</td>
<td>TMP-SMZ, ceftriaxone; then clarithromycin</td>
<td>6</td>
<td>Pneumonia resolved</td>
</tr>
<tr>
<td>2</td>
<td>[7]</td>
<td><em>Streptomyces</em></td>
<td>Pneumonia, sepsis</td>
<td>Blood</td>
<td>None</td>
<td>Penicillin, sulfadiazine, streptomycin, aureomycin</td>
<td>1</td>
<td>Pneumonia resolved</td>
</tr>
<tr>
<td>3</td>
<td>[8]</td>
<td><em>Streptomyces</em></td>
<td>Pneumonia</td>
<td>Bronchoscopic specimen</td>
<td>HIV infection'</td>
<td>Cefuroxime, amikacin; then amoxicillin/ clavulanate</td>
<td>1</td>
<td>Pneumonia resolved</td>
</tr>
<tr>
<td>4</td>
<td>[9]</td>
<td><em>Streptomyces</em></td>
<td>Pneumonia, monoarthritis</td>
<td>Bronchial washings, knee aspirate</td>
<td>HIV infection'</td>
<td>Piperacillin/ tazobactam; then imipenem</td>
<td>NA</td>
<td>Resolution of pneumonia, arthritis, and fever in 4–5 d</td>
</tr>
<tr>
<td>5</td>
<td>[13]</td>
<td><em>Streptomyces</em></td>
<td>Pericarditis</td>
<td>Pericardial biopsy specimen</td>
<td>None</td>
<td>Oxacillin, drainage</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>[14]</td>
<td><em>S. griseus</em></td>
<td>Brain abscess</td>
<td>Abscess</td>
<td>None</td>
<td>Penicillin, streptomycin, oxytetracycline, drainage</td>
<td>3</td>
<td>Abscess resolved</td>
</tr>
<tr>
<td>7</td>
<td>[15]</td>
<td><em>S. somaliensis</em></td>
<td>Peritonitis</td>
<td>Abscess</td>
<td>None</td>
<td>Sulfadiazine, Vancomycin, gentamicin; then amikacin, imipenem</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>[16]</td>
<td><em>Streptomyces</em></td>
<td>Endocarditis</td>
<td>Blood</td>
<td>Prosthetic aortic valve</td>
<td>Sulfafoxime, Vancomycin, gentamicin; then amikacin, imipenem</td>
<td>6</td>
<td>NA</td>
</tr>
<tr>
<td>9</td>
<td>[17]</td>
<td><em>Streptomyces</em></td>
<td>Lymphadenitis</td>
<td>Cervical lymph node</td>
<td>HIV infection'</td>
<td>TMP-SMZ</td>
<td>NA</td>
<td>Progressive wasting for 15 mo</td>
</tr>
</tbody>
</table>

NOTE. NA = data not available; TMP-SMZ = trimethoprim-sulfamethoxazole.

* CD4 cell count, $>400/mm^3$.

' CD4 cell count, $100/mm^3$.

' CD4 cell count, $122/mm^3$.

' Poor dentition noted, believed to be the route of infection.

' CD4 cell count, $83/mm^3$.

*Mycobacterium tuberculosis* isolated from lymph node as well; patient also treated with isoniazid, rifampin, and nystatin.
Invasive streptomyces infection may be more common than these isolated case reports suggest. Many *Streptomyces* species have been found in clinical isolates, most commonly *S. griseus* and *S. somaliensis* [5, 18, 19]. The reference laboratory of the CDC has summarized the characteristics of aerobic actinomycetes sent for species identification and susceptibility testing between October 1985 and February 1988. *S. griseus* represented 7.7% of the clinical isolates, following only *Nocardia* and *Actinomadura* species in frequency [18]. Unfortunately, because of the lack of clinical information regarding these isolates, it is not known whether *S. griseus* was a primary pathogen. However, the frequency of *S. griseus* in the latter study suggests that streptomyces infections are underreported.

Because of the paucity of well-documented cases, treatment recommendations for streptomyces infections must be based on in vitro data [18, 19] and analogies from treatment of nocardia infections [20]. In the CDC evaluation of aerobic actinomycetes, a spectrum of antimicrobials were tested against *S. griseus* [18]. On the basis of in vitro MICs and expected serum concentrations, the most active drugs appeared to be minocycline, imipenem, erythromycin, and doxycycline, with >80% of strains susceptible. The aminoglycoside tested in this study appeared to have very favorable MICs as well. We used a macrolide for therapy in our patient on the basis of this in vitro data as well as the susceptibilities obtained from the CDC.

It is of interest that 29% of the *S. griseus* strains in the above study were resistant to TMP-SMZ. This finding may be important because TMP-SMZ is often considered the drug of choice for treatment of nocardiosis. In the event that pathology could be attributed to an actinomycte and the laboratory distinction between actinomyctes has not yet been made, TMP-SMZ may not be the best choice. Aminoglycosides, however, appear to have very effective MICs for actinomyctes and may be appropriate for first-line therapy.

Because of these in vitro results and the limited clinical experience, the best treatment options for visceral streptomyces infection might be macrolides, minocycline, doxycycline, ceftriaxone, amikacin, or imipenem. In contrast to the treatment of nocardiosis, TMP-SMZ may not be optimal treatment for invasive infection with *Streptomyces* species [18]. Recommendations for duration of treatment of streptomyces infections can only be extrapolated from experience with the treatment of nocardiosis. Given the good results of therapy for nocardiosis [20], a 6–12-month course of antibiotics should be adequate for treatment of invasive streptomyces infection. Clearly, further experience with invasive streptomyces infection is necessary to delineate the course of infection, treatment, and outcome.

References

18. McNeil MM, Brown JM, Jarvis WR, Ajello L. Comparison of species distribution and antimicrobial susceptibilities of aerobic actinomycetes sent for species identification and susceptibility testing between October 1985 and February 1988. *S. griseus* represented 7.7% of the clinical isolates, following only *Nocardia* and *Actinomadura* species in frequency [18]. Unfortunately, because of the lack of clinical information regarding these isolates, it is not known whether *S. griseus* was a primary pathogen. However, the frequency of *S. griseus* in the latter study suggests that streptomyces infections are underreported.

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