Thoracic Vertebral Actinomycosis: *Actinomyces israelii* and *Fusobacterium nucleatum*

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Abstract

*Actinomyces* spp. is considered a rare pathogen in today’s medicine, especially with thoracic vertebral involvement. Classic actinomycosis (50%) presents as an oral-cervicofacial (“Lumpy Jaw“) infection. This report describes a case of spinal cord compression caused by *Actinomyces israelii* with coisolation of *Fusobacterium nucleatum*. There are limited numbers of similar cases.
Case Report

Introduction

This case involves a 43 year old Filipino male who presented to a medical center emergency department with a chief complaint of acute lower back pain and urinary incontinence. He had been in his usual state of health until approximately three days prior to admission when he first noticed a gradual onset of bilateral lower extremity weakness followed by difficulty with walking, and finally inability to arise from bed. In addition, the patient stated that he had been experiencing low grade fevers and progressive weight loss over the past several months. His past medical history was unremarkable and did not include any recent trauma. The patient emigrated from the Philippines to Hawaii about 20 years ago. However, he denied any history of exposure to tuberculosis or any recent travel history back to the Philippines or South East Asia.

In the emergency room the patient appeared disoriented although he was able to follow simple commands. His vital signs included a temperature of 97.8 F, blood pressure 121/75, heart rate of 116/min, and mild tachypnea with an O2 saturation of 99% on room air. On physical examination, he was noted to have poor dentition with evidence of multiple previous dental extractions. Neurologic examination revealed significant bilateral lower extremity weakness (2 out of 5) with brisk deep tendon reflexes, positive ankle clonus, and positive Babinski signs, as well as diminished rectal tone. The remainder of the physical exam was unremarkable. Laboratory blood findings were significant for a leukocytosis (22.0 x 10^9/L) with 87% segmented neutrophils, an elevated platelet count of 722 x 10^6/L, and an erythrocyte sedimentation rate of 84 mm/hr. An HIV-1/2 antibody screen was negative. The remaining labs were non-
contributory. A chest x-ray showed a left lower lobe infiltrate with minimal pleural effusion.

Because of the possibility of spinal cord compression and injury, the patient was admitted to the medical intensive care unit for further workup and management. This included an MRI of the spine, which showed an abnormal signal intensity involving the thoracic vertebrae from T5 thru T8 and an abnormal soft tissue mass enhancement consistent with an apparent abscess involving the left posterior chest wall and ribs, extending to the thoracic vertebral column, and into the epidural space with apparent spinal cord compression. A CT scan of the chest revealed similar abnormal findings involving the left posterior chest wall and ribs as well as a collapsed left lower lobe with minimal pleural effusion. A bone scan also showed increased activity within the thoracic vertebrae and left ribs with no mention of bony erosion. The patient was started empirically on IV antibiotics, consisting of ceftriaxone at 2 gram every 24 hours and vancomycin at 1 gram every 12 hours, as well as dexamethasone. This was followed immediately by an emergent thoracic laminectomy and debridement of the epidural abscess. A very thick fibrinous material was present overlying the dura and several pockets of gross purulence were seen from T5 to the superior aspect of T9. There was a well organized abscess running over the entire extent of exposure and tapering at the rostral and caudal ends. Aerobic and anaerobic cultures of the abscess fluid were obtained intraoperatively, collected in a BBL Port- A-Cul Envelope (BD, #221607) and transported to the Microbiology Laboratory. The wound was then irrigated with a copious volume of antibiotic containing saline and closed. The culture was positive for both
Actinomyces spp. and Fusobacterium spp. Blood and urine cultures showed no growth. Stains for acid-fast bacilli and mycobacterial cultures were also negative.

The patient’s antibiotic regimen was changed to IV penicillin G at 2 million units every 4 hours and Clindamycin at 600 mg every 6 hours. Post-operatively, the surgical wound healed well without the expression of purulence. The patient’s bilateral lower extremity motor strength markedly improved during his remaining hospital course. However, residual bowel and urinary dysfunction still persisted. He was subsequently transferred to a rehabilitation center for 6 weeks of IV antibiotic therapy consisting of Penicillin G and Clindamycin. This was followed by twelve months of oral amoxicillin at 500 mg tid.
Materials and Methods

Culture Isolation and Microscopy

A gram stain was used to identify the microscopic morphology of the isolates. Culture was performed using Brucella Agar as the primary anaerobic media. The RapidANA II system (API) was used in the biochemical identification of the anaerobe.

PCR and Sequencing

The isolate was confirmed using 16S rRNA gene sequencing. A fragment of the 16S rRNA gene was amplified from DNA extracted from the bacterial isolate by PCR using the *Pfu* DNA polymerase, PCR reaction mix and the universal eucaryotic primers 27F and 1492R. Thermal cycling conditions consisted of denaturation at 94°C for 3 min, followed by 30 cycles at 94°C for 45s, 55°C for 45s, and 72°C for 90s. Final extension was carried out at 72°C for 7 min, followed by cooling to 4°C. The PCR product was then purified using the Qiagen PCR purification kit (Qiagen) and sequenced with the following primers: 27F (AGAGTTTGATCMTGGCTCAG), 530R (GTA TTA CCG CGG CTG CTG), 981R (GGG TTG CGC TCG TTG CGG G), 1492R (TACGGYTACCTTGTTACGACTT). DNA Sequencing was performed using the BigDye terminator cycle sequencing kit (3.1v) and was resolved on a ABI 3730XL DNA Analyzer (Applied BioSystems, Foster City, CA). The full 16S rDNA sequences were then assembled in Seqman (DNASTAR). Sequence analysis was performed using ChromasPro (v1.33, Technelysium Pty Ltd.) and a Blast search (www.ncbi.nlm.nih.gov/blast/Blast.cgi).
Results

Anaerobic culture of the epidural abscess resulted in both *A. israelii* (Figure 1A) and *Fusobacterium nucleatum* (Figure 1B). *Fusobacterium spp.* are non-spore forming and nonmotile. The classic microscopic description for *Fusobacterium spp.* is a gram negative, spindle shaped bacillus as revealed by this isolate and shown in Figure 1B (10). The identification of *Fusobacterium nucleatum* was confirmed using the RapidANA II system (API). Both bacteria are commonly found as a part of the normal flora in the human oral cavity. However, it should be noted that once disruption of the mucosa occurs, they can contribute to the development of a systemic anaerobic infection.

*Actinomyces spp.* are gram positive branching bacilli, which often present with a beaded appearance on Gram stain (10). They are characteristically identified as non-motile, non-spore forming, non-acid fast, and facultative anaerobes. These features were present in the isolate for this case. Culture isolates can be presumptively identified from both microscopic and macroscopic appearance as outlined in the algorithm in Figure 2. This algorithm was constructed by one of us (MJB) from characteristics described in authoritative microbiology reference textbooks (10, 17). However, definitive identification relies upon complex phenotypic testing (i.e. carbohydrate fermentation, enzyme profiles or gas chromatography) or 16S rRNA sequencing. This isolate was identified from the primary anaerobic culture (Brucella agar) using both phenotypic and genotypic approaches. The isolate only grew anaerobically and exhibited the typical “molar tooth” appearance as demonstrated on a sheep blood agar plate (Figure 1A).

The isolate was identified as *A. israelii* with a base identity homologus to *A. israelii* strain A1 (AF479270.1) at 889/891 (99.8%).
Discussion

Classic actinomycosis is well documented as an oral-cervicofacial (i.e. Termed appropriately as “Lumpy Jaw“) lesion, accounting for approximately 55% of the actinomycosis cases (2). Other sites of infection manifest as thoracic (15%), abdominal and pelvic (20%), musculoskeletal (rare) and central nervous system (rare) disease. However, actinomycosis has rarely been described in the involvement of thoracic vertebral bone (20).

Disruption of mucosal membrane is essential for the formation of actinomycosis. Once Actinomyces invades tissue into disrupted mucus membrane, it slowly expands and develops into an abscess. Classic actinomycosis usually occurs following trauma, dental procedures or other such surgical procedures where these bacteria may reside as normal flora.

Several risk factors exist for the development of actinomycosis. It occurs more commonly in males without a clear explanation. Other risk factors may include poor oral hygiene and the use of intrauterine devices (IUD’s). In addition, immunocompromised and other conditions, such as diabetes, alcoholism, immunosuppressive infections (e.g. HIV), and steroid use are thought to predispose individuals to the development of actinomycosis (1, 4, 8, 19, 22).

The diagnosis of actinomycosis requires a high clinical suspicion, since Actinomyces spp. is an insidious organism and may only show nonspecific clinical manifestation (e.g. Low grade fever or other constitutional symptoms) (22, 24). Even in a patient with thoracic vertebral actinomycosis, the clinical appearance does not differ remarkably from
other diseases causing spinal cord compression such as malignancy or epidural abscess (6, 22, 24).

Actinomyces was originally discovered in 1877 as a genus containing the causative agent of actinomycosis in cattle. Thereafter, in 1891 *A. israelii* was first isolated from a lung abscess by Wolff and Israel (1, 22). Since that time, other *Actinomyces spp.* and related bacteria have been isolated and are believed to be involved in a wide variety of human infections. Oral infections have been classically linked to *A. israelii*. However, a number of other species have also been involved in human infection. These include *A. meyeri, A. graevenitzii, A. turicensis, A. gerencseriae, A. odontlyticus, A. cardiffensis, A. radingae, A. naeslundii, other Actinomyces spp., and a closely related species, Varibaculum cambriensis* (17, 22).

Actinomycosis is frequently isolated with other bacteria including *Fusobacterium spp., Bacteroides spp., Capnocytophaga spp., Eikenella spp., Staphylococcus spp., Streptococcus spp.* and *Enterococcus spp.* (1,22). Although the relationship between co-isolation of these organisms and their role in the pathogenesis of actinomycosis still remains unclear, concomitant organisms may play an important role in reducing oxygen tension, making it more conducive for anaerobes. The coexistence of those organisms may be related to both a common source and their facilitation of the growth and development of actinomycosis (11).

Vertebral involvement of actinomycosis is usually secondary to an infection of contiguous tissue rather than hematogenous spread. (6). Likewise, it is unlikely to be the result of vertebral osteomyelitis and epidural abscess due to common bacterial pathogens.
A search of the literature from 1950 to 2007 reveals a total of only 14 other cases of thoracic vertebral actinomycosis. The present case is the fifteenth. These cases are listed in Table 1 (3, 6, 7, 9, 12, 13, 16, 18, 23, 24, 25, 26, 27). In summary, they show that 9/15 (60%) were caused by \(A.\ textit{israelii}\), with an average age of 42.2 years, 12/14 (85.7%) occurred in males and at least 8/12 (66.7%) were associated with thoracic involvement or other pulmonary symptoms. In addition, 7/15 (46.7%) revealed a co-isolation of another organism(s). Epidemiological data in these cases were consistent with those of other non-thoracic cases, even where the details were not well documented.

Actinomycosis is sometimes difficult to differentiate from mycobacterial disease (both \textit{M. tuberculosis} and non-\textit{M. tuberculosis}) or \textit{Nocardia asteroides} due to the similarity in clinical manifestations and bacterial morphology (6, 21, 22, 24). Identification of the organism is critical, since the choice of antimicrobial agent(s) differ in the treatment for each bacterial pathogen and may impact both patient morbidity and mortality. In addition, \textit{Actinomyces spp.} is slow growing and anaerobic, thus optimal specimen collection requires an anaerobic culture and extended growth (possibly 14 to 21 days). A proposed scheme for the identification of \textit{Actinomyces spp.} is described in Figure 2.

Treatment of actinomycosis includes antimicrobial therapy with or without surgery. Penicillin is the antibiotic of choice, although other antimicrobial agents such as clindamycin, tetracycline or erythromycin can be used in cases of penicillin allergy (14, 15). Optimal duration of antimicrobial therapy should be tailored depending on the severity of illness. However, a longer duration with antimicrobial agents is usually necessary since premature termination of antimicrobial therapy may cause a relapse of actinomycosis (5). Conventional therapy dictates a duration of 6 to 8 weeks with an
intravenous antimicrobial agent followed by 6 to 12 months with an oral antimicrobial agent. In the cases listed in Table 1, 7/15(46.7%) received six months or more of antibiotic treatment.

The patient presented in this case study was diagnosed with thoracic vertebral actinomycosis due to *A. israelii*. It is not known how much *Fusobacterium nucleatum* contributed to the infection or the role of this anaerobe in the pathogenesis of actinomycosis. However, as suggested by others, it may be reasonable to consider the *F. nucleatum* as a potential copathogen in treatment (20). The most likely disease progression was probably from an extension of a primary lung infection (itself caused by aspiration of oral flora) followed by destruction of ribs, development of empyema, and subsequent paraspinal abscess formation. The main risk factors in the patient’s history were a history of alcoholism and poor dentition.
Conclusion

Actinomyces spp. is often found as normal flora of the oral, gastrointestinal and vaginal track. Actinomycosis can virtually develop at any site. Due to the slow development of infection, attention to risk factors and careful physical examination is especially important in certain procedures (e.g. dental examination) in order to detect and treat in the early stage of actinomycosis. Since the hallmark of infection is the formation of an abscess, surgical treatment may also be necessary regardless the site of infection in order to prevent spread of the disease.

Emphasis should be placed on having a high clinical suspicion and using appropriate techniques to obtain adequate specimen for a successful diagnosis of actinomycosis. The patient’s symptoms in this case improved with surgical decompression and antimicrobial therapy. However, the patient did not fully recover from urinary and bowel impairment despite appropriate treatment. Since actinomycosis with thoracic vertebral column involvement is rarely encountered and reported, actinomycosis should be considered in patients with spinal cord compression with risk factors regardless of their clinical manifestation(s).

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Table 1  Cases of actinomycosis with thoracic vertebral involvement.

<table>
<thead>
<tr>
<th>Age &amp; Gender</th>
<th>Actinomyces Species</th>
<th>Year</th>
<th>Other Bacteria Cultured</th>
<th>Risk Factor or Diagnosis</th>
<th>Country</th>
<th>Duration of Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>43/M</td>
<td>A. israelii</td>
<td></td>
<td>Current Case</td>
<td>Fusobacterium nucleatum</td>
<td>United States (U.S.)</td>
<td>6 weeks of IV PenicillinG with IV clindamycin 12 months amoxicillin</td>
</tr>
<tr>
<td>51/M</td>
<td>A. israelii</td>
<td>2006</td>
<td>None</td>
<td>Pneumonia</td>
<td>Israel</td>
<td>8 weeks of IV penicillin G 12 months of amoxicillin</td>
</tr>
<tr>
<td>50/F</td>
<td>A. israelii</td>
<td>2006</td>
<td>Bacteroides melaninogenicus</td>
<td>None</td>
<td>India</td>
<td>12 weeks of oral ofloxacin with rifampin</td>
</tr>
<tr>
<td>38/M</td>
<td>A. israelii</td>
<td>2006</td>
<td>Fusobacterium spp.</td>
<td>Alcohol abuse Cerebral involvement</td>
<td>Denmark</td>
<td>8 weeks of IV metronidazole with IV penicillin G 12 months of amoxicillin</td>
</tr>
<tr>
<td>32/M</td>
<td>A. israelii</td>
<td>2000</td>
<td>None</td>
<td>Mediastinal involvement</td>
<td>China</td>
<td>6 weeks of IV Penicillin G 6 months of oral penicillin V</td>
</tr>
<tr>
<td>34/F</td>
<td>Actinomyces spp.</td>
<td>1998</td>
<td>Actinobacillus actinomycetem comitans</td>
<td>None</td>
<td>France</td>
<td>12 weeks of oral ofloxacin with rifampin</td>
</tr>
<tr>
<td>33/M</td>
<td>Actinomyces spp.</td>
<td>1998</td>
<td>None</td>
<td>None</td>
<td>Japan</td>
<td>3 weeks of piperacillin 5 weeks of oral erythromycin</td>
</tr>
<tr>
<td>46/M</td>
<td>Actinomyces spp.</td>
<td>1990</td>
<td>None</td>
<td>Pneumonia Alcohol abuse</td>
<td>U.S.</td>
<td>6 weeks of IV Penicillin G 12 months of oral penicillin G</td>
</tr>
<tr>
<td>56/M</td>
<td>A. israelii</td>
<td>1989</td>
<td>None</td>
<td>9 months cough</td>
<td>United Kingdom (U.K.)</td>
<td>5 weeks of IV clindamycin 3 weeks of oral clindamycin</td>
</tr>
<tr>
<td>40/M</td>
<td>A. meyeri</td>
<td>1989</td>
<td>None</td>
<td>Lung involvement</td>
<td>Denmark</td>
<td>6 weeks of penicillin G 12 months of oral penicillin V</td>
</tr>
<tr>
<td>31/M</td>
<td>A.israelii</td>
<td>1981</td>
<td>Propionibacterium acnes Enterococcus spp.</td>
<td>Cough</td>
<td>U.S.</td>
<td>Penicillin G (Not stated duration) 6 weeks of oral penicillin V</td>
</tr>
<tr>
<td>45/M</td>
<td>A.israelii</td>
<td>1979</td>
<td>Actinobacillus actinomycetem comitans</td>
<td>Dental work</td>
<td>U.S.</td>
<td>Penicillin G and oral ampicillin (Not stated duration)</td>
</tr>
<tr>
<td>52/M</td>
<td>A. israelii</td>
<td>1979</td>
<td>Actinobacillus actinomycetem comitans</td>
<td>Lung involvement</td>
<td>U.S.</td>
<td>8 weeks of IV penicillin G 12 months oral penicillin V</td>
</tr>
<tr>
<td>42/M</td>
<td>A. bovis</td>
<td>1960</td>
<td>None</td>
<td>Cough Rib osteomyelitis</td>
<td>U.K.</td>
<td>3 weeks of IV penicillin G</td>
</tr>
<tr>
<td>42/N/S*</td>
<td>Actinomyces spp.</td>
<td>1951</td>
<td>None</td>
<td>Lung involvement</td>
<td>U.K.</td>
<td>N/S*</td>
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N/S* Not indicated.
REFERENCES


Figure 1  *Actinomyces israelii* “molar tooth” appearance on sheep blood agar and microscopic morphology showing branching gram positive bacilli (A). *Fusobacterium nucleatum* (larger colony) and *A. israelii* (smaller colony) colony morphology on sheep blood agar and microscopic morphology showing “fusiform” gram negative bacillus for *F. nucleatum* (B).
Figure 2  Algorithm for the identification of gram positive, non-sporeforming, branching/pleomorphic bacilli.