Disseminated Coinfection with *Actinomyces graevenitzii* and *Mycobacterium tuberculosis*: Case Report and Review of the Literature

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We report the first case of disseminated infection with both *Actinomyces graevenitzii* and *Mycobacterium tuberculosis* and review the medical literature. Concomitant actinomycosis and tuberculosis is very rare. The potential of the facultatively aerobic, newly described *A. graevenitzii* for disseminated invasive infection needs to be evaluated.

Most infections with *Actinomyces* spp. are polymicrobial (19). The copathogens are most commonly colonizers of the respective involved organ systems. They act synergistically by inhibiting host defense mechanisms and/or reducing oxygen tension in the affected tissue, which enhances growth of *Actinomyces* spp. (19). We present a unique case of concomitant disseminated actinomycosis and tuberculosis and a review of the medical literature.

A 46-year-old African-American male presented with a 4-week history of fever, night sweats, a productive cough, and a 30-pound weight loss. He denied any chest pain, shortness of breath, or hemoptysis. He was not aware of any sick contacts, and he had not been incarcerated or homeless.

His past medical history was significant for coronary artery disease, hypertension, and chronic congestive heart failure. There were no known drug allergies and no current drug, tobacco, or alcohol use. He admitted to smoking crack cocaine years ago. There was no travel history nor exposure to animals nor recreational or professional outdoor activities.

Three weeks prior to this admission, he had been seen for the same symptoms and was discharged after computed tomography (CT) of the chest with a presumptive diagnosis of community-acquired pneumonia and treated with doxycycline.

His physical exam on admission was within normal limits except for a temperature of 39.1°C and severe periodontal disease. Abnormal laboratory parameters were a sodium level of 129 mmol/liter, an albumin level of 2.8 g/dl, microcytic anemia with a hemoglobin level of 10.4 g/dl (MCV, 72.6 fl), and a platelet count of 596,000/μl. He denied any chest pain, shortness of breath, or hemoptysis. He was not aware of any sick contacts, and he had not been incarcerated or homeless.

A CT of the abdomen showed fluid collections with contrast enhancement in the right perihilar area (Fig. 2A) and in the cul de sac between rectum and bladder (Fig. 2B). The liver did not show any lesions on CT.

Needle aspirates from both abscesses again showed numerous acid-fast bacilli, identified as *M. tuberculosis*, upon Ziehl-Neelsen staining (Fig. 3A) and many filamentous gram-positive rods (Fig. 3B). Aerobic and anaerobic cultures remained without growth.

After 6 months of antituberculous therapy and oral ampicillin, the patient underwent a repeat CT that showed complete resolution of all lesions in the lung (Fig. 1C) and abdomen.

The Gram stain of the expectorated sputum sample on admission was read as normal oropharyngeal flora, with >25 leukocytes and 10 to 25 epithelial cells per low-power field (grade 4 according to the Barlett Grading System) (11). The aerobic culture (37°C at 5% CO₂) showed heavy growth of gram-positive rods in long chains. The colonies on the chocolate agar plate had a characteristic “molar tooth” appearance (Fig. 3C). No sulfur granules were seen in the sputum. The organism was initially identified by the hospital laboratory as *Actinomyces* spp. on the basis of Gram stain characteristics, colony morphology, and commercial biochemical testing (RapID ANA II; Innovative Diagnostic Systems, Inc., Atlanta, GA). The isolate was then sent to a reference laboratory. Upon repeat biochemical testing, the isolate was reidentified as a *Bifidobacterium* spp.
For definitive identification, the DNA of the isolate was subjected to 16S rRNA gene sequencing via PCR. The sequence data were analyzed by assembling the forward and reverse sequences into a consensus sequence. This consensus sequence was edited to resolve discrepancies between the two strands by evaluation of the electropherogram. For an accurate determination of species similarities, the 5' and 3' ends were cut at identical positions along the gene. Finally, the consensus sequence was compared with a database available on MicroSeq 1.4 (Applied Biosystems, Inc.) and also a Mayo Clinic Foundation database containing wild-type strains and well-characterized patient specimens. The patient's isolate sequence was aligned with its related type strain sequences using BIOEDIT v. 5.0.9 (Department of Microbiology, North Carolina State University: http://www.mbio.ncsu.edu/bioedit/bioedit.html). The resulting multiple sequence alignment was used to construct the phylogenetic tree with the unweighted pair group method using arithmetic averages algorithm and a distance matrix estimate with WET (Windows Easy Tree 1.31, developed by J. Dopazo; available at http://www.tdi.es/programas/WET.html). As shown in Table 1, the isolate is most closely aligned with *Actinomyces graevenitzii*, with 1.3% divergence from a reference strain.

The mycobacterial sputum culture on admission eventually grew *Mycobacterium tuberculosis* (identification by Accuprobe, GenProbe Inc., San Diego, California). Standard susceptibility testing showed that it was fully susceptible to isoniazid, rifampin, ethambutol, and pyrazinamide.

![CT scans of the thorax. A: 3 weeks prior to admission, showing a right paratracheal mass. B: on admission, showing a right-upper-lobe cavernous lesion with surrounding airspace disease. C: complete resolution of all pulmonary lesions after 6 months of antibacterial and tuberculostatic therapy.](image1)

![CT of the abdomen, revealing fluid collections with contrast enhancement in the right quadratus lumborum muscle (A) and in the cul de sac between rectum and bladder (B).](image2)
of infection with *Actinomyces* spp., by coinoculation of *Eikenella corrodens* in an animal model has been reported (3). Coaggregation of *Actinomyces* and *Streptococcus* spp. leads to increased resistance to phagocytosis in a mouse peritonitis model (13, 14).

The most common copathogens for thoracic actinomycosis are *Actinobacillus actinomycetemcomitans*, *Streptococcus* spp., and *Haemophilus* spp. (19).

Disseminated actinomycosis presents a special challenge to clinicians by presenting with prolonged, multisystem manifes-

![Figure 3](image-url)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Present case</th>
<th>Stein et al. (22)</th>
<th>Chakravarty and Fernandez (2)</th>
<th>Lee (9)</th>
<th>Bates and Cruickshank (1)</th>
<th>von Arnim (23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient 1</td>
<td>Patient 2</td>
<td>Patient 1</td>
<td>Patient 2</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>43</td>
<td>12</td>
<td>22</td>
<td>30</td>
<td>35</td>
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<td>City and state or country</td>
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<td>Delhi, India</td>
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<td>New York, N.Y.</td>
<td>Leicester, UK</td>
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<tr>
<td>Ethnicity</td>
<td>African-American</td>
<td>African-American</td>
<td>Asian Indian</td>
<td>Asian Indian</td>
<td>African-American</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Coronary artery disease, hypertension</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>HIV infection</td>
<td>No</td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unknown</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Site(s) of infection</td>
<td>Lung cavity, soft tissue</td>
<td>Lung cavity, costal osteitis</td>
<td>Lung cavity</td>
<td>Bilateral lung cavities</td>
<td>Lung cavity</td>
<td>Lung cavity, subternal abscess</td>
</tr>
<tr>
<td>Identification on Gram stain</td>
<td>Yes (only soft tissue)</td>
<td>Yes (from thoracic wall abscess)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes (from pleural empyema)</td>
<td>Yes (from wall abscess)</td>
</tr>
<tr>
<td>Identification by culture</td>
<td>Yes (only lung)</td>
<td>Yes (from thoracic wall abscess)</td>
<td>Yes (from sputum)</td>
<td>Yes (from sputum)</td>
<td>Yes (from pleural empyema)</td>
<td>Yes</td>
</tr>
<tr>
<td>Actinomyces species</td>
<td>A. graevenitzai</td>
<td>A. israelii</td>
<td>A. israelii</td>
<td>A. israelii</td>
<td>Not reported</td>
<td>A. israelii</td>
</tr>
<tr>
<td>Treatment for actinomycosis</td>
<td>Amoxicillin for 6 mo</td>
<td>Penicillin IV for 2 mo, PO for 1 mo</td>
<td>Penicillin IV for 3 mo</td>
<td>Penicillin IV for 3 mo</td>
<td>Not reported</td>
<td>Unknown</td>
</tr>
<tr>
<td>Treatment for tuberculosis</td>
<td>RIPE for 2 mo, RI for 4 mo</td>
<td>INH, ethambutol, rifampin</td>
<td>Streptomycin and INH for 3 mo, INH and PAS for 18 mo</td>
<td>Streptomycin and INH for 10 wk</td>
<td>Unknown tuberculosis treated 4 yr before diagnosis of actinomycosis</td>
<td>Unknown</td>
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<tr>
<td>Surgery</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Lung resection</td>
<td>Thoracoplasty</td>
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<tr>
<td>Outcome</td>
<td>Healed</td>
<td>Recovered</td>
<td>Recovered</td>
<td>Recovered</td>
<td>Recovered</td>
<td>Died from amyloidosis</td>
</tr>
</tbody>
</table>

Abbreviations: RIPE, rifampin-isoniazid-pyrazinamide-ethambutol; IV, intravenously; PO, orally; INH, isoniazid; PAS, para-aminosalicylic acid; UK, United Kingdom.
tations mimicking other diseases. In a recent review, predomin-
antly, A. meyeri, A. israeli, and A. odontolyticus were identi-
fied in cases of disseminated disease (4).

A. graevenitzii was first isolated from four clinical human spec-
imens (three respiratory and one bone sample) in 1997 by a
Swedish group (18). Like the other Actinomyces spp., it is a
nonmotile, branched, and nonsporulating gram-positive rod
which is catalase negative and facultatively anaerobic and has
a distinct biochemical profile (18, 21). It has been recently
identified in the saliva of infants (20).

In contrast to other microorganisms, M. tuberculosis seems
to play only a minor role as a copathogen in actinomycosis. We
performed a PubMed search with the term “actinomyces” or
“actinomycosis” combined with the term “tuberculosis.” Addi-
tionally, we searched review articles and medical textbooks on
actinomycosis.

The clinical features of the cases found in the literature are
shown in Table 2. In total, seven cases could be located in the
English literature. Of note, all isolates with reported species
information were A. israelii, but information about the exact
method of identification was often lacking. All patients had
fever and thoracic infection, and most of the isolates were
recovered from respiratory specimens. None of the cases had
disseminated disease. Actinomycosis coinfection with M. tuber-
culosus was “rarely encountered” in Holm’s series of 960 clin-
cial isolates (7).

Other than these seven cases in the English literature, there
are scattered case reports of coinfection from Russia and Po-
land (3, 5, 6, 8, 10, 15–17). These journals were not available
for review.

To our knowledge, this case represents the first report of
coinfection with A. graevenitzii and M. tuberculosis. It is also
the first clinical description of disseminated infection with A. grae-
venitzii.

The presence of both organisms was well documented in a
respiratory specimen of the diseased lung as well as in distant
metastatic abscesses, defining this as disseminated infection.
Although A. graevenitzii did not grow in the abscess fluid or in
the blood culture, a typical morphology was seen on the Gram
stain from the abscess fluid. Growth of microorganisms seen
on the Gram stain can be significantly impeded after 10 days
of appropriate therapy. Molecular diagnostic techniques would
have been needed as evidence for true disseminated infection
with this organism. The presence of a coinfection was recog-
nized in a timely fashion, preventing further, possibly invasive
diagnostic studies. Without the addition of a β-lactam antibi-
otic, the patient would most likely have suffered a prolonged
hospital course.

The rarity of actinomycotic and tuberculous coinfection re-
ports in the literature is striking and gives rise to several ques-
tions. Firstly, respiratory specimens are most likely cultured
aerobically, which will negatively select most Actinomyces spp.

In the original study of A. graevenitzii, isolates grew on blood
agar at 37°C with 5 to 10% CO₂ (18), like the specimen from
our patient.

Second, Actinomyces spp. are commensals of the mouth cav-
ity and the upper respiratory tract. Their presence in respira-
tory specimens does not necessarily signify clinical disease and
may often not be reported. In our case and the cases described
in the literature, a significant disease process was identified.

We postulate that preexisting periodontal disease was the
source of infection, with spread to the lungs by aspiration and
subsequent hematogenous dissemination to distant soft tissues.
M. tuberculosis was most likely acquired by contact with an
infected individual in the community.

Third, the disseminated nature of the coinfection makes our
case somewhat unique. Since little is known about the patho-
physiology of A. graevenitzii infection, we can only speculate
about factors that explain its dissemination. From the host
perspective, our patient did not show any key conditions, such
as severe immunosuppression or malnutrition, predisposing to
overwhelming disease.

The fourth point of discussion is the identification of clini-
cally important Actinomyces species. As pointed out by
Sarkonen et al. (21), differentiation of these bacteria is a dif-
cult and costly process which is most likely not done in the
routine laboratory. Also, many of the recently discovered spe-
cies included in the genus Actinomyces are not included in most
commercial identification kits.

An interesting theory for the rarity of actinomycotic and
tuberculous coinfection was pointed out by Nikiforchin (12),
who suggested that there are properties of Actinomyces spp.
that are inhibitory to growth characteristics of M. tuberculosis.
This has not been confirmed in other studies.

Resistance to antimycobacterial drugs is a common cause of
therapeutic failure in cases of tuberculosis. In the setting of full
susceptibility, other entities such as coinfection might be sus-
pected and appropriate cultures obtained. Coinfection of M.
tuberculosis and Actinomyces spp. is rare and therefore pre-
sents a diagnostic challenge in clinical practice. Early identifi-
cation prevents costly and prolonged diagnostic and therapeu-
tic interventions.

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matrix analyses.

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