Case report

Mixed *Actinomyces israelii* and *Aggregatibacter actinomycetemcomitans* infection causing empyema necessitatis and multiple skin abscesses in an immunocompetent patient

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SUMMARY

A 45-year-old man presented with left chest wall pain, swelling and cough. Over a 2-month period he developed abscesses in the right foot, right anterior thigh, left buttock and left chest. Incision and drainage of the soft tissue abscesses and video-assisted thoracoscopic surgery to drain the loculated empyema contiguous with the chest wall abscess were performed as surgical management. Gram stain showed beaded Gram-positive rods and the culture initially grew *Aggregatibacter actinomycetemcomitans* and *Eikenella corrodens*. Pathological evaluation of the pleura showed sulfur granules and organisms consistent with *Actinomyces spp.* on Gomori methenamine silver stain; *Actinomyces israelii* was recovered in culture with extended incubation. The patient was treated for 3 weeks with ceftriaxone and oral metronidazole, followed by oral amoxicillin. Culture of *A. actinomycetemcomitans* with other findings consistent with actinomycosis warrants 6–12 months of antibiotic therapy.

BACKGROUND

Aggregatibacter actinomycetemcomitans is a Gram-negative bacillus known to cause periodontitis, skin abscess, osteomyelitis and endocarditis.

Despite its name, it is not commonly known to clinicians that *A. actinomycetemcomitans* is classically found as part of a polymicrobial infection with *Actinomyces spp.* We herein report a successfully diagnosed case of thoracic actinomycosis in a patient with multifocal abscesses.

CASE PRESENTATION

A 45-year-old man with a past medical history of hypertension, alcohol abuse (30 beers a day, in remission for 5 months) and tobacco abuse (40 cigarettes per day) presented with worsening left-sided chest pain, swelling and cough. Two months prior to admission, he noticed a small abscess on his right dorsal forefoot. The abscess was drained by his physician and treated for 10 days with amoxicillin and doxycycline. He subsequently developed a second abscess on his right anterior thigh that opened and drained spontaneously. Three weeks prior to admission, he developed a third abscess in his left buttock. Two weeks prior to admission, he developed a fourth abscess on his left lateral chest wall, for which he was prescribed doxycycline and amoxicillin-clavulanate. Though the pain in the left buttock improved, he developed worsening left chest-wall pain and cough despite antibiotics.

He had been in the military until 5 years earlier and had been stationed around the world but he denied any recent travel or drug use including injection drug use. Initial vitals were a blood pressure of 143/76 mm Hg, heart rate of 120 beats/min, respiratory rate of 18/min temperature of 37°C (98.6°F) and oxygen saturation on room air of 98%. Oral examination revealed poor dental hygiene without obvious dental caries or broken teeth. Lung examination showed moderate crackles at the left chest. Skin examination demonstrated four different skin abscesses. Lesion #1 was an erythematous, indurated lesion of approximately 3×6 cm at the left chest wall around the area of the fifth rib at the middle axillary line with the central area of drainage (figure 1). The other three skin abscesses were on the dorsum of the right foot, on the anterior right thigh and at the left gluteal base, respectively. Otherwise, cardiac and abdominal examination were unremarkable.

Figure 1 An erythematous, indurated, 3×6 cm lesion at the left chest wall around the area of the fifth rib at the anterior axillary line with the central area of drainage.

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Figure 2 CT of chest with contrast showed large area of focal inflammatory fatty stranding in the subcutaneous fat of the left chest wall with direct extension and associated inflammatory oedema of the left chest wall musculature. Additional heterogeneous fluid is seen in the adjacent pleural space and associated extensive airspace consolidation in the left lung and immediately beneath.

INVESTIGATIONS

Laboratory tests revealed elevated white blood cell count of $17\,700/\mu\text{L}$ (normal range $3700\text{--}10\,500/\mu\text{L}$), blood urea nitrogen of 7 mg/dL (normal range $10\text{--}20\text{ mg/dL}$) and creatinine

Figure 3 Thoracoscopic view of the inflamed lung adherent to the chest wall, vascular fibrosis and areas of fibropurulent inflammation.

Figure 4 A: Pleural and soft tissue biopsy demonstrated sulfur granules with Gomori methenamine silver (dense aggregates of Gram-positive, filamentous, non-spore-forming rods, consistent with *Actinomyces spp.*) (40X objective); B: On Gram stain (100X objective) rods were beaded and Gram positive; C: In culture these organisms grew slowly as classic 'molar tooth' colonies (anaerobic blood agar at 12-days incubation).

of 0.4 mg/dL (normal value $0.6\text{--}1.2\text{ mg/dL}$). CT of the chest with contrast showed a large area of inflammation of all soft tissue layers of the left chest wall including intercostal muscles. Heterogeneous loculated fluid was seen under the inflamed chest wall with contiguous extensive airspace consolidation of the adjacent left lung (figure 2). CT of the abdomen/pelvis revealed a large, left buttock inflammatory phlegmon with reactive inflammation of the left gluteus muscle. No CT of the thigh or the right foot was done.

TREATMENT

The patient was diagnosed with four skin abscesses with one extending into the left lung cavity with empyema. Three sets of blood cultures were obtained and the patient was started on vancomycin and ceftriaxone. Thoracic and general surgery teams were consulted. Drainage of the loculated empyema on the left, drainage of the left chest wall abscess, aspiration of the gluteal abscess and incision and drainage of the right anterolateral thigh abscess were performed. The loculated empyema on the left was drained by video-assisted thoracoscopic surgery that, in addition, demonstrated dense adhesions of the lung to the chest wall with areas of fibro purulent inflammation (figure 3). Specimens were obtained for microbiology and surgical pathology.

OUTCOME AND FOLLOW-UP

Gram stain of the abscess material showed beaded Gram-positive rods. Aerobic cultures grew *Aggregatibacter actinomycetemcomitans* and *Eikenella corrodens* within 5 days. Blood cultures remained negative. A transesophageal echocardiogram was performed to rule out endocarditis, and it did not show any vegetations. Pathological examination of the surgical specimens showed sulfur granules and organisms consistent with *Actinomyces spp.* on Gomori methenamine silver stain (figure 4-A and B). Due to suspicion of actinomycosis, anaerobic cultures were incubated for an extended period of time. Classic 'molar tooth' colonies were noted on anaerobic blood agar at 12-days incubation (figure 4-C) and these were identified as *Actinomyces israelii* on day 16 using the Bruker BioTyper MALDI-ToF system (Bruker; Billerica, MA). Ultimately, this patient was diagnosed with thoracic actinomycosis causing empyema necessitatis. Antibiotics were changed to ceftriaxone and metronidazole. His four abscesses and cough gradually improved with antibiotics after the surgery and he was discharged with a plan to continue therapy with intravenous ceftriaxone and oral metronidazole for

3 weeks after the surgery, followed by oral penicillin for actinomycosis for a total of 12 months.

DISCUSSION

A. actinomycetemcomitans is a Gram-negative, fastidious, coccoid or rod-shaped bacillus formerly known as *Actinobacillus actinomycetemcomitans*.^{1,2} It is an opportunistic pathogen and a component of normal oral flora strongly associated with periodontitis, and can cause endocarditis, bacteremia, polymicrobial wound infections, brain abscesses, endophthalmitis, glomerulonephritis, septic arthritis, pneumonia, empyema, cardiac device infections, spinal epidural abscess and osteomyelitis.^{3–5} *A. actinomycetemcomitans* is a member of the 'HACEK' group of bacteria, which includes [*H*]aemophilus, [*A*]ggregatibacter (previously *Actinobacillus*), [*C*]ardibacterium, [*E*]ikenella, and [*K*]ingella, which collectively cause 3% of all cases of infective endocarditis.³ As its name suggests, *A. actinomycetemcomitans* was first isolated by Klinger in 1912 as a coisolate with *A. israelii* in cases of cervicofacial actinomycosis, and has since been identified as a coisolate in many cases of cervicofacial actinomycosis.^{1,6} Surgical pathology from our patient showed sulfur granules with beaded Gram-positive rods.

Sulfur granules contain a collection of bacteria at the centre surrounded by inflammatory debris, and oval basophilic masses with eosinophilic clubs at the fringes. Granules can be seen in other infections such as nocardiosis, chromoblastomycosis, and botryomycosis. However, the finding of beaded Gram-positive rods along with sulfur granules strongly suggests a diagnosis of actinomycosis.⁷ Of note, *Nocardia* is a Gram-positive rod as well but it is a strict aerobe that exhibits partial acid fast staining and does not cohort with other organisms; so this helps us differentiate it from actinomycosis.

While it was initially isolated in conjunction with *A. israelii*, monomicrobial cultures of *A. actinomycetemcomitans* have been reported from sites such as blood, brain or lung.^{5,8,9} *A. actinomycetemcomitans* is usually susceptible to cephalosporins, fluoroquinolones, aminoglycosides, azithromycin, rifampin, trimethoprim-sulfamethoxazole, chloramphenicol and tetracycline.¹⁰ Most strains show complete or partial resistance to clindamycin, semisynthetic penicillins, erythromycin and vancomycin.¹¹ Many of the isolates do not grow well (in one report, 60% of HACEK-group isolates failed to grow for susceptibility testing) and empirical treatment may be necessary.¹² Beta lactamases are rarely present in *A. actinomycetemcomitans*¹³ and negative beta lactamase testing permits use of a penicillin in isolated infections as well as *Aggregatibacter/Actinomyces* co-infections. Duration of treatment for isolated *Aggregatibacter* infection depends on the diagnosis and clinical response to treatment. While the treatment may be in the order of weeks to months, it usually does not require long-term treatment (up to 1 year) like actinomycosis does.

Actinomyces are slow-growing organisms and are found as normal flora in the human oropharynx, gastrointestinal tract and urogenital tract.⁷ When the mucosa is breached, the organism gains access to deeper tissues and causes an indolent, slowly progressing granulomatous disease broadly categorised as orocervicofacial actinomycosis and abdominopelvic actinomycosis.¹⁴ This can mimic a number of other conditions, the most common being malignancy and it requires a high degree of clinical suspicion to make the diagnosis of actinomycosis. Orocervicofacial actinomycosis is the most common form of the disease and comprises about 50% of all reported cases.¹⁵ Thoracic actinomycosis accounts for 15% to 20% of the cases.^{15,16} Rarely,

a progressing thoracic infection may extend into extra thoracic tissues, and form an abscess on the thoracic wall resulting in pus eroding through the chest wall, causing 'empyema necessitatis'.¹⁴

Actinomycosis is usually diagnosed by recovering the organism in culture. Labs are unable to recover the organisms from culture in over 50% of cases. This is likely due to previous antibiotic treatment, overgrowth of concomitant organisms or inadequate anaerobic transport and culture techniques.¹⁷ Cultures need to be held for much longer than for typical bacterial organisms since the organism is slow-growing. If actinomycosis is suspected, the lab needs to be alerted to trigger appropriate anaerobic collection techniques and a longer incubation (2 to 3 weeks) of the sample under strict anaerobic or microaerophilic conditions to increase culture yield.⁷

Actinomyces spp. are almost invariably isolated as part of a polymicrobial flora which include *A. actinomycetemcomitans*, *E. corrodens*, *Fusobacteria*, *Bacteroides*, *Capnocytophaga*, *Staphylococci*, *Streptococci* or *Enterobacteriaceae*.¹⁸ *Actinomyces* are susceptible to a wide range of antimicrobial agents. Recent studies in Europe demonstrated that most were susceptible to β lactams (including benzylpenicillin, amoxicillin, ceftriaxone, meropenem and piperacillin/tazobactam), doxycycline, clindamycin, erythromycin, linezolid and clarithromycin,^{19,20} whereas fluoroquinolone susceptibility was mixed. The duration of antibiotic treatment depends on the initial burden of the disease, performance of surgical resection/debridement, and the patient's response to treatment.²¹ In some refractory cases, additional surgical drainage or excision is required. Generally, a total of 6–12 months of treatment with antibiotics is recommended for actinomycosis. Mortality rate is reported between 0% to 28% depending on the site of infection and the time to diagnosis. The highest mortality has been reported in actinomycosis with central nervous system involvement.²²

It is very important to suspect *Actinomyces* if *A. actinomycetemcomitans* is grown in culture specimens from patients with a compatible clinical history, given that treatment duration can change from a few weeks for monomicrobial *A. actinomycetemcomitans* infection to 6–12 months for concurrent actinomycosis. Though infections purely from *A. actinomycetemcomitans* have been reported, growth of *A. actinomycetemcomitans* with sulfur granules and beaded Gram-positive rods on Gram stain warrants high degree of suspicion for *Actinomyces* and demands extended culture duration for confirmation followed by appropriate treatment.

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Learning points

- *Aggregatibacter actinomycetemcomitans* is a Gram-negative, fastidious, coccoid or rod-shaped bacillus known to cause periodontitis, endocarditis, polymicrobial wound infections, brain abscesses, pneumonia, spinal epidural abscess and osteomyelitis.
- Growth of *A. actinomycetemcomitans*, especially with co-existing sulfur granules and/or beaded Gram-positive rods on Gram stain warrants high degree of suspicion for coinfection with *Actinomyces* spp.
- Incubation of specimens under strict anaerobic conditions for a minimum of 14 days (up to 21 days) is recommended for increasing culture yield of *Actinomyces*.
- Actinomycosis requires prolonged antibiotic therapy for 6–12 months.
- Penicillin remains the mainstay of therapy for *Actinomyces* infections.

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