Achromobacter xylosoxidans Infection Presenting as a Pulmonary Nodule Mimicking Cancer

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Achromobacter xylosoxidans is typically isolated from pulmonary sources, presenting as pneumonia in immunosuppressed individuals. We describe a novel clinical presentation of A. xylosoxidans infection presenting as multiple spiculated, pulmonary nodules mimicking cancer for which the patient underwent a wedge resection of the lung for diagnosis and staging of presumptive cancer.

CASE REPORT

A 73-year-old immunocompetent male patient was referred to the pulmonary service at Madigan Healthcare System in Tacoma, WA, in June, 2008 by his ophthalmologist for pulmonary nodules found in 2008. He obtained a chest radiograph as part of an evaluation for sarcoidosis which was considered a possible cause of new-onset uveitis following cataract surgery. His symptoms included an intermittent, nonproductive cough and mild exertional dyspnea. He denied any fevers, weight loss, or chest pains. His medical history was otherwise notable for moderate chronic obstructive lung disease with a 30-pack/year history of smoking. He underwent a noncontrast computed tomography (CT) of the chest, which showed a macrolobulated 11- by-13-mm nodule in the apical segment of the right upper lobe, a 7- by-13-mm pleura-based macrolobulated nodule in the anterior segment of the left upper lobe, and a 6- by-8-mm nodule adherent to the anterior wall of the left mainstem bronchus. The spiculated lesions were highly suspicious for carcinoma; however, the differential diagnosis included infectious etiologies, including atypical mycobacteria or fungal organisms, given his history of living in both the Midwest and Southwest at various times of his life. A positron emission tomography (PET) scan performed 1 month later showed that his nodules were not metabolically active. Further evaluation included sputum cultures for bacteria, fungi, and acid-fast bacilli, all of which were negative. He subsequently underwent a fiber optic bronchoscopy with repeated cultures and cytology, all of which were nondiagnostic. After discussing surgical resection versus radiographic follow-up of the nodules, the patient opted for a short-term interval CT scan of the chest.

Approximately 18 months after the nodules were first identified, repeat imaging revealed development of spiculated changes to the right upper lobe nodule. To cover for potential infectious etiologies, the patient was treated with a single course of levofloxacin and azithromycin over the course of his surveillance. The patient noticed an approximate 8- to 9-lb weight loss, and repeat imaging with a PET scan revealed a new nodule adjacent to the previously noted nodule in the right upper lobe. The decision was made to proceed with surgical resection.

Tissue from the right upper lobe wedge resection was sent first for histology and showed acute and chronic inflammation and necrosis. No evidence of malignancy was identified. The tissue was then sent for microbiological analysis. No organisms were identified by the initial Gram stain. Many (>100) colonies of an oxidase-positive, catalase-positive, nonfermenting Gram-negative rod were isolated after overnight incubation in a 6% CO2 atmosphere. The organism was initially identified as Cupriavidus pauculus by the Vitek 2 GNI card (bioMérieux, Durham, NC) at a confidence level of 94.24%. Since C. pauculus is an unusual isolate, the API 20 NE (bioMérieux) strip was used to confirm the identification; in this instance, though, the isolate was identified as Burkholderia cepacia. Because of this discrepancy, we performed 16S rRNA gene sequencing. Nucleic acid was extracted by suspending a colony in 200 μl of molecular-grade deionized water. Bacterial cells were lysed by heating for 10 min at 99°C. The lysed cells were centrifuged for 10 min, and 3 μl of the supernatant was then used for PCR.

Primers VAB1 (TGGAGAGTTTGATCCTGGCTCA), VAB2 (GTATTACCGCGGCTGCTGG), VAB3 (CCAGCAGCCCGGTATAATAC), VAB4 (CGGGACCTTACCAACATCTC AC), VAB5 (GTGAGATTTGGGTATGGAATCCGG), and VAB6 (AAGGAGGTTGATCCAGCGCGCA) were utilized to sequence a large portion of the 16S rRNA gene in five separate reactions in the following pair subsets: VAB-1/2, VAB-3/4, VAB-5/6, VAB-1/4, and VAB-3/6. PCR assays were performed as previously described (23). The resulting PCR products were cleaned with ExoSAP-IT (USB Products, Cleveland, OH) and sent to a core sequencing lab for cycle sequencing. The resulting sequences (VAB1/VAB2, 504 bases; VAB3/VAB4, 450 bases; VAB5/VAB6, 450 bases; VAB1/VAB4, 996 bases; VAB3/VAB6, 923 bases) were assembled into a 1,500-base sequence that was analyzed using the BIBI, NCBI, and Microseq databases. This sequence matched the type strain of Achromobacter xylosoxidans in the Microseq database at all...
bases except at positions 436 and 448, as determined by the neighbor-joining method and concise analysis.

First described by Yabuuchi and Ohyama in 1971 after being isolated from ear discharge in patients with chronic otitis media, \textit{A. xylosoxidans} is included in the family \textit{Alcaligenaceae} (45, 46). \textit{A. xylosoxidans} is an aerobic, motile, Gram-negative bacterium that is a nonfermenter and is catalase and oxidase positive. \textit{A. xylosoxidans} is ubiquitous in aqueous environments and has been associated with well water (36), tap water (17, 43), and swimming pools (33) as well as environmental bodies of water (41). It is also a prevalent nosocomial colonizer and has been isolated from multiple types of aqueous solutions found in the health care setting, such as nonbacteriostatic saline (24), dialysis solutions (33), contact lens solutions (15), intravenous CT contrast solutions (32), chlorhexidine gluconate solutions (35), and ultrasound gel (28). \textit{A. xylosoxidans} also colonizes fomites such as mechanical ventilators (6), neonatal incubators (25, 29), faucet aerators (17, 43), intravenous catheters (1, 17, 20, 24), epidural catheters (30), urinary catheters (29), intravascular pressure transducers (17), pacemaker leads (2, 26, 33, 36), and extracorporeal membrane oxygenation machines (21). \textit{A. xylosoxidans} is widely considered to be an opportunistic bacterium with low virulence. It is most often isolated in adults with comorbidities and/or indwelling medical devices and in neonates (15). Cases of \textit{A. xylosoxidans} infections have been documented affecting a wide range of patient ages, from 3 days to 87 years old (17, 29). The most common predisposing underlying medical issues observed in the setting of \textit{A. xylosoxidans} infection are malignancy, both hematologic and solid organ (30%), cardiac disease (21%), and immunosuppression (27%) (3, 9, 17, 18, 20). Other documented comorbidities include HIV infection, cystic fibrosis (CF) (10, 13, 17, 33, 40), diabetes mellitus (DM) (1, 6), chronic renal failure (CRF) (6), chronic obstructive pulmonary disease (COPD) (12), cirrhosis (17), intravenous drug abuse (41), treatment with high-dose corticosteroids (3), rheumatoid arthritis with immunomodulation therapy (37), and underlying urologic abnormalities (38).

While primary, uncomplicated bacteremia is the most common manifestation of \textit{A. xylosoxidans} infection, this organism has been associated with a wide range of clinical infections (9). \textit{A. xylosoxidans} has been isolated in cases of ear and eye infections (26, 28, 30), urinary tract infections (28, 38), intra-abdominal infections (39), liver abscesses (4), soft tissue infections (5, 29), osteomyelitis (42), arthroplasty infections (37), meningitis (8, 26, 29, 30), ventriculitis (35), endocarditis (1, 2, 41), and pneumonia (3, 10–13, 20, 32, 34, 39, 44). \textit{A. xylosoxidans} has been isolated from multiple sources, including blood (3, 9, 11, 16, 18, 28, 33), cerebrospinal fluid (CSF) (8, 26, 29, 30), stool, urine (28, 38), sputum (40), skin, ear discharge (29, 45), wounds (29), abscesses (4, 39), bone (42), joints (37), endocardium (1, 2, 41), ascites fluid (39), and corneal scrapings and vitreous humor fluid (14, 22, 27, 31).

A significant proportion of \textit{A. xylosoxidans} infections are polymicrobial, with reports varying from 15 to 52% of cases (3, 9, 17, 28). \textit{A. xylosoxidans} infections clinically present with nonspecific symptoms of fever, chills, anorexia, and lethargy; however, up to 20% of cases may also develop skin lesions (9, 31).

While \textit{A. xylosoxidans} is generally considered to be of low virulence, immunocompromised patients infected with this organism can experience significant rates of morbidity and mortality. Mortality rates of up to 80% have been reported in infections of \textit{A. xylosoxidans} in neonates (9). The case mortality rate is reported to be as high as 30% in adult cases of bacteremia and up to 65% in cases of meningitis, endocarditis, and pneumonia (9, 44). Gomez-Cerezo et al. identified risk factors associated with increased mortality to include older age (over 65 years) and neutropenia (17).

Pulmonary cases of \textit{A. xylosoxidans} have not been previously documented in patients without associated comorbidities (Table 1). Pulmonary cases of \textit{A. xylosoxidans} infection have been associated with a myriad of underlying medical problems, including IgM deficiency (11), hematologic malignancies, including acute myelogenous leukemia (AML) (18, 34), solid organ malignancies (20, 39), COPD (12), and CF (10, 13, 39, 44) (Table 1). In one study, \textit{A. xylosoxidans} was the most common Gram-negative nonfermenter in CF patients, second only to \textit{Pseudomonas aeruginosa} (13). It is thought that \textit{A. xylosoxidans} represents a colonizer of older cystic fibrosis patients, with a mean age of colonization of 18.4 years, similar to that of \textit{B. cepacia} (10).

Our case also reflects the general tendency of this bacterium to be misdiagnosed when relying solely on biochemical identification techniques, first being identified as \textit{C. pauculus} by the Vitek II GNI card and then as \textit{B. cepacia} with the API 20 NE strip. \textit{A. xylosoxidans} was misidentified in up to 11% of cases, according to one study (33). When misdiagnosed, \textit{A. xylosoxidans} is most often falsely identified as nonpigmented strains of \textit{Pseudomonas aeruginosa} or \textit{B. cepacia} (34). In light of this propensity for misidentification, sequencing offers a more reliable method of definitive diagnosis (19).

\textit{A. xylosoxidans} is characteristically resistant to all aminoglycosides and rifampin while expressing variable resistance to trimethoprim-sulfamethoxazole, ciprofloxacin, and other quinolones (3, 17, 20, 29, 39). Most isolates are generally susceptible to carbapenems and antipseudomonal penicillins (3, 17).
Currently, there are no specific standardized sensitivities for this organism, although MIC interpretive criteria for "Other Non-Fermenters" from CLSI document M100-S21 may be used; there are no disk diffusion interpretive criteria for these organisms (7). Etest strips (bioMérieux, Durham, NC) were used to determine MICs for the isolate of A. xylosoxidans from this study for the following antibiotics: ceftazidime (MIC, 8 μg/ml, sensitive), ceftriaxone (MIC, 64 μg/ml, resistant), gentamicin (MIC, 24 μg/ml, resistant), meropenem (MIC, 0.19 μg/ml, sensitive), imipenem (MIC, 1.5 μg/ml, sensitive), and ciprofloxacin (MIC, 4 μg/ml, resistant). While there are no disk diffusion interpretive criteria for A. xylosoxidans, growth of the isolate up to the disk occurred for the following antibiotics: ampicillin, ampicillin/sulbactam, cefazolin, ceftriaxone, and gentamycin. In the case of our patient, the surgical resection of the pulmonary nodules was deemed curative, and no evidence of recurrence has been observed to date. Other than the empirical therapy (levofloxacin, amoxicillin-clavulanic acid, doxycycline, and azithromycin) initially used for treatment of this patient’s infection, specific antimicrobial treatment was not used. Sensitivities were not tested for the antibiotics used for empirical therapy, and it is possible that the isolate was resistant to each of these agents or that the antimicrobials did not penetrate to the site of infection in high-enough concentrations to clear the infection before surgical resection was attempted.

While Achromobacter xylosoxidans is a prevalent waterborne nosocomial organism and cause of infection or colonization in those with comorbidities, it has not previously been reported as a cause of multiple asymptomatic spiculated lung nodules, mimicking cancer. Also, this case highlights the necessity of employing sequence in the diagnosis of A. xylosoxidans due to its propensity to be misidentified when identification is based on phenotypic techniques alone.

Nucleotide sequence accession number. The 1,500-base sequence of the A. xylosoxidans isolate was deposited in GenBank under accession number HQ676601.

The views expressed in this paper are those of the authors and do not reflect the official policy or position of the Department of the Army, the Department of Defense, or the U.S. Government.

REFERENCES