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Case report

A pediatric case of fever of unknown origin and pericarditis associated with actinomyces pneumonia

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ABSTRACT

We describe a rare case of *Actinomyces meyeri* pneumonia in a pediatric patient. Our patient was admitted twice for recurrent pericarditis in the setting of persistent fevers, initially thought to be secondary to Coxsackie B virus. She was treated with colchicine and ibuprofen, as well as a short course of oral steroids. Patient was admitted a third time for acute respiratory failure and was found to have a large right empyema and pleural effusion requiring chest tube placement. After extensive multi-specialty workup, *A. meyeri* was isolated from chest tube culture. Patient's intravenous (IV) antibiotics were subsequently narrowed to ampicillin, and she was discharged.

1. Introduction

Up to 34% of actinomycosis cases are found in the thorax [1]. *Actinomyces meyeri* is one of the commonly isolated species of bacteria and may be even more prevalent than *A. israelii* in patients with pneumonia [2,4]. Actinomycosis can also involve the pericardium as purulent pericarditis in a child and cardiac tamponade in an adult have been described [3,4].

Actinomyces are found in oral flora, gastrointestinal tracts, and vaginal tracts, and underlying causes of pneumonia include poor dental hygiene, oral surgery, difficulty swallowing, and foreign bodies [5–7]. Other predisposing factors include immunosuppression including from medical therapy, developmental delay, seizures, tracheostomy, and leukemia; however, some studies show that most patients do not have comorbidities [8,9].

Actinomyces pneumonia can be very difficult to diagnose, and in one retrospective analysis of 145 patients, only five patients had the correct initial diagnosis [9]. The main symptoms are non-specific: weight loss, cough, expectoration, bloody sputum, fever, fatigue, night sweats, chest pain, and hemoptysis [8,9]. This disease can be mistaken for tuberculosis, a fungal infection, or tumor [10]. Radiological presentation is non-unique with features from pneumonia to cavitation to pleural involvement [11].

2. Case report

A three-year-old previously healthy, fully vaccinated female presented to the emergency department for the third time after a two-week history of recurrent fevers of unknown origin with associated back and abdominal pain (Table 1). Her exposure history was notable for attending daycare and living with her family on a rural farm with livestock on a well water system. She had initially presented to the emergency department (ED) twice in the preceding two weeks for the same complaints, thought secondary to a viral illness. At this third presentation, she was found to have significantly elevated inflammatory markers. An abdominal ultrasound revealed a small left sided pleural effusion. Patient was admitted for further workup. EKG showed diffuse ST elevations consistent with acute pericarditis, and echocardiogram showed significant circumferential pericardial effusion without tamponade. Cardiology and Rheumatology services were consulted. Computerized tomography (CT) scan of the chest showed small bilateral pleural effusions. Blood cultures were negative. Urine cultures grew 40,000 col/mL *Actinomyces turicensis* and 2000 col/mL of *Staphylococcus simulans*, thought secondary to contamination, thus no antibiotics were initiated. Coxsackie B antibody titers were positive at 1:80. She was treated with ibuprofen and furosemide, and repeat echocardiogram showed interval improvement in the size of her pericardial effusion. She defervesced and was discharged home on ibuprofen and furosemide. One week after discharge, repeat echocardiogram demonstrated trivial residual

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Table 1
ED visit and admission timeline.

Hospital Visit	Days from First ED Visit	Duration of Stay (Days)
ED Visit 1	0	< 1
ED Visit 2	6	< 1
ED Visit 3 (1st Admission)	11	5
ED Visit 4 (2nd Admission)	35	1
ED Visit 5 (3rd Admission)	46	19

effusion, thus ibuprofen and furosemide were discontinued.

Ten days after follow-up, patient presented to the ED for the fourth time with recurrent fevers and was found to have worsening inflammatory markers. Repeat echocardiogram had significantly increased pericardial effusion. She was re-admitted, colchicine was initiated and both ibuprofen and furosemide were restarted. Additional tests were obtained, including ANA, ANCA, anti-ds DNA, Invitae autoinflammatory panel, Coccidiomycosis screen, and QuantiFERON TB Gold. She showed no symptom progression and was discharged home the day after. She was kept on colchicine, furosemide, and ibuprofen.

At follow-up three days later, she was still noted to have recurrent daily fevers. Given concern for an evolving systemic autoimmune process, she was started on a five-day course of prednisone (1 mg/kg daily) in addition to continuing ibuprofen and colchicine. A repeat echocardiogram two days later was normal. Coccidiomycosis screen, ANA, ANCA, and anti-ds DNA results were negative. QuantiFERON TB Gold was indeterminate, thus a T-spot was advised but not obtained at that time.(Table 2).

Two days after the completion of her steroids, patient presented to the ED for the fifth time still with persistent fevers and now in acute respiratory distress. Initial labs at presentation were notable for a leukocytosis of 35,300/mm^3, elevated procalcitonin of 0.65 ug/L, and elevated C-reactive protein (CRP) of 23.7 mg/dL; however, erythrocyte sedimentation rate (ESR) was decreased at 47 mm/h, as was her B-type natriuretic peptide (BNP) at 121 pg/mL compared to 326.1 pg/mL previously. Complete metabolic panel (CMP) was grossly normal except for an elevated alanine aminotransferase (ALT) of 110 U/L. EKG was only notable for sinus tachycardia, hence echocardiogram was not repeated given low concern for recurrent pericardial effusion with interval improvement in BNP. Given persistence of fevers on this fifth visit, Infectious Disease was eventually consulted.

Blood cultures were obtained, and she was started on vancomycin and cefepime. Chest x-ray (CXR) demonstrated a large opacity throughout the right hemithorax with cavitary lesion, which was not seen on previous CXRs. Further characterization on chest ultrasound showed a homogenous hypoechoic pleural effusion without septations and new complete atelectasis of the right lung. She was subsequently admitted to the PICU.

Chest tube was inserted and 500 mL of malodorous, purulent output was drained. Pleural fluid cultures were obtained. Findings on follow-up CT chest were suggestive of empyema with moderate right sided hydropneumothorax. Final autoimmune workup was negative (Table 3). Blood cultures grew *S. epidermidis* in ½ bottles, thought to be a contaminant as repeat blood cultures were negative. Preliminary pleural fluid showed many white blood cells, gram positive cocci, gram negative cocci, gram negative rods, and gram positive rods, some of which appeared to be branching. Vancomycin and cefepime were discontinued, and she was narrowed to ampicillin and sulbactam. Her home dose of colchicine was also continued.

Table 2
Trend of WBC, hemoglobin, CRP and ESR from patient's first admission, up to the day of discharge from her third admission.

	1st admission	2nd admission	3rd admission	One week prior to discharge	Day of discharge
WBC (10 *3/mcL)	14.3	28.6	35.3	12.6	9.8
Hemoglobin (g/dL)	9.7	10.4	10.4	7.5	8.4
CRP (mg/dL)	11.6	20.5	23.7	2.0	3.7
ESR (mm/hr)	112	92	47	90	82

Table 3
Autoimmune work up and results.

C3	214.2 mg/dL
C4	36.3 mg/dL
ANA	Negative
ANCA	Negative
Anti DNA (DS) Ab	< 1 IU/mL
Invitae Autoinflammatory and Autoimmunity Syndrome Panel	Increased risk allele in NOD2; VUS in ITGB2, RBCK1, and RNASEH2C

Initial immunologic work up (Table 4) were within normal limits. CXR supported pneumatocele versus pneumothorax. Given possible pneumatocele, hyper-IgE syndrome was considered, however IgE levels were also normal. Patient improved and by day 3 she was transferred to the acute care floor.

Approximately one week following admission, her pleural fluid cultures were finalized as growing pan-sensitive *A. meyeri,* and antibiotics was further narrowed to ampicillin alone. Other infectious workup were largely negative. Due to concerns for underlying immunodeficiency, T-spot test with a Candida control was done. Both PPD and Candida control were negative, prompting further immunologic workup. Oxidative burst was within normal limits, however CH50 activity was absent and AH50 activity was low (Table 4). Because of concern the colchicine may be causing some degree of immunosuppression, it was discontinued after a normal repeat echocardiogram.

Her hospital course was complicated by development of normocytic anemia likely secondary to chronic disease. Fevers resolved by week two of admission, and she was discharged by week three on IV ceftriaxone to complete a total 6 week course of IV antibiotics, followed by 6–12 months of oral antibiotics. Following discharge, she was referred to Immunology. A repeat CH50 activity performed two months after was subsequently normal. The remainder of her immune work up was also within normal.

3. Discussion

Our case presents a previously healthy child with *Actinomyces meyeri.* Diagnosis was delayed, which is typical, as mean length of illness prior to diagnosis is 5.3 months [12]. CXR did not show definite signs of pneumonia until the fifth ED visit. The organism causing the pneumonia was confirmed only after a week-long culture from the chest tube, further delaying the diagnosis. This bacteria takes a lengthy period of time to culture, including up to 21 days in anaerobic conditions [13]. In reported cases of actinomyces pneumonia, it is rarely the initial diagnosis made, as it does not grow well in culture and other infectious and non-infectious processes can imitate actinomycosis [9,10]. Additionally, the *A. turicensis* that grew in the patient's urine culture was assumed to be a contaminant because it can also be normal genital flora [6].

The patient's ultimate diagnosis is a rare and unusual presentation in this age group, where it is most often associated with poor dentition

Table 4
Immunology work up and results.

IgE	< 25 IU/mL
IgG	899 mg/dL
IgA	158.2 mg/dL
IgM	148.4 mg/dL
Absolute CD3 + Cells	2315 cells/uL
Absolute CD19 + Cells	1840 cells/uL
Neutrophile Oxidative Burst	96% at 72 h
AH50	54 units/mL
CH50	0 units/mL

[14]. It was noted during outpatient follow-up that the patient was last seen by her dentist a year prior and did not tolerate the dental exam at that time.

Bacteria may have been the underlying cause of the patient's pericarditis. We reviewed a case report of cardiac tamponade in an adult with A. *meyeri* following pericarditis as well as a case of purulent pericarditis in a child [3,4]. In the adult's case, analysis of the pericardial fluid grew no microorganisms, so it was assumed *A. meyeri* was the underlying cause of the tamponade. In the child's case, the pathology of the pericardium showed purulence and sulfur granules.

The viral Coxsackie B infection could have been coincidental, as the titer came back 1:80, or it could have primed the patient for a post-viral infection. Enteroviruses have been isolated in patients with bacterial pneumonia [15]. For instance, there was a case in a child who had Hemophilus influenzae pneumonia with Coxsackie A9 found in the pericardial fluid [16]. Also, it is commonly known that respiratory viruses such as influenza can lead to secondary bacterial pneumonia due to increased susceptibility to and attachment of bacteria in virus affected cells, destruction of the mucosal layer, and decreased neutrophil attraction [17,18]. A similar, unknown, mechanism may be extrapolated to cause susceptibility to pneumonia from the Coxsackie B virus.

Colchicine or steroid use may also have contributed to a transient immunosuppression in the patient. Colchicine is a drug that modulates innate immunity, primarily through tubulin disruption [19]. Neutrophil chemotaxis, adhesion, and superoxide production are all inhibited. Macrophage function is also disrupted. As colchicine may cause leukopenia, it has been associated with pneumonia, and a study in gout patients showed 42% increase in hazard of pneumonia in patients who took colchicine [20]. Our patient's complete blood counts showed leukocytosis and normal neutrophil oxidative burst with an initial absent CH50 activity. Given this, colchicine may have been a minor contributor to her Actinomyces infection. Instead, the patient's condition notably worsened when she was given a course of prednisone, as relayed by her father. It is possible that steroids exacerbated a preexisting actinomyces infection; however, that was only a five-day course. Steroid use is consistent with leukocytosis (Fig. 1).

4. Conclusion

A rare case of Actinomyces pneumonia associated with pericarditis was seen in our patient who initially presented with fever of unknown origin. We believe increased awareness of this presentation may make diagnosis easier in the future, as there have been a paucity of cases described in the literature. Given the long average time span before commencement of symptoms and determination of diagnosis, patients presenting similarly should be examined for poor dentition and checked with Coxsackie B virus titers. Imaging methods such as echocardiography and CT of the chest are also encouraged.

Providers should be cautious when giving immunosuppressive medication such as colchicine or steroids to patients with a presentation as seen in our patient. Given that the patient's course markedly worsened after a course of steroids, we suspect that an underlying subacute Actinomyces pneumonia infection was exacerbated by this medication. An Infectious Disease specialist would be advantageous in evaluating patients with a similar presentation and potentially recommending further evaluation prior to steroid use. This might prevent future patients from progressing from subacute to acute infection with Actinomyces and/or lead to earlier diagnosis. Contributing all symptoms to a viral illness with low titers in a patient with a similar presentation could lead to early closure and delayed diagnosis .

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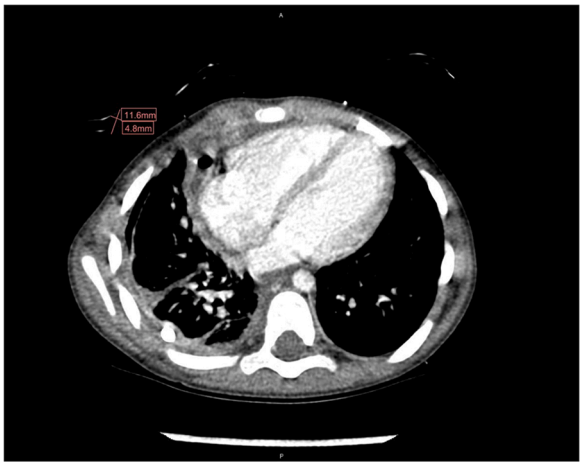

Fig. 1. CT chest image from PICU admission demonstrating an area of rim-enhancing fluid along the right aspect of the mediastinum inferiorly measuring about 1.2 × 0.5 cm.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Ara Albert Alexanian – data collections, data analysis, writing; **Rhobe Brager**, MD – data collections, writing; **Maria Concepcion Mendoza**, MD – data collections, literature review; **Rhonda Keoshkeyan**, MD – study design, data analysis, writing.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

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