An 11-Year-Old Boy with Diffuse Pulmonary Infiltrates and Respiratory Failure

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An 11-year-old African-American boy with no significant medical history presented to the emergency department (ED) with a 1-week history of dry, non-productive cough associated with shortness of breath and headaches. No history of fevers, vomiting, diarrhea, throat or ear pain, or recent travel was noted. The

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Figure 1. Chest X-ray of the patient at the time of initial presentation. Note the bibasilar opacities and diffuse infiltrates in upper zones.

For diagnosis, see page 183

Editor’s note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
Case Challenge

The patient’s older brother had upper respiratory tract infection symptoms 1 week prior that resolved spontaneously with no treatment. Two days before the patient’s presentation, he was seen by his pediatrician and had been prescribed oral azithromycin and albuterol.

In the ED, tachycardia (heart rate of 125 beats per minute) and hypoxia (oxygen saturation of 86% on room air) were noted. The patient’s saturations improved to 99% after starting supplemental oxygen. Physical exam was notable for the presence of bibasilar bronchial breath sounds with fine crackles over the upper lobes and decreased air entry in the lower lobes. There was no lymphadenopathy and no digital clubbing.

Initial investigations included a chest X-ray that was significant for coarse, near-confluent airspace opacities involving bilateral lower lobes, the right middle lobe, and lingula (Figure 1). C-reactive protein and erythrocyte sedimentation rate were both mildly elevated (4.6 mg/L and 16 mm/hour, respectively). Complete blood count, electrolytes, viral studies, and capillary blood gas were normal. The patient was started on ceftriaxone and azithromycin.

Six days after admission, the patient was still hypoxic and showed no clinical improvement. At this time, he was also started on amphotericin B to empirically treat for a possible fungal infection. A flexible bronchoscopy and bronchoalveolar lavage (BAL) were performed. The bronchoscopy showed normal airway anatomy, and BAL showed lymphocytic predominance. Cultures were negative for bacterial, fungal, and mycobacterial organisms. Direct fluorescent antibody tests for influenza, parainfluenza, legionella, adenovirus, and cytomegalovirus were all negative. A computed tomography (CT) scan of the chest (Figure 2) revealed bilateral opacities with interstitial thickening, as well as enlarged para-tracheal, subcarinal, and right hilar lymph nodes. The patient underwent extensive screening for immunodeficiency, as well as enlarged para-tracheal, subcarinal, and right hilar lymph nodes. The patient underwent extensive screening for immunodeficiency, as well as enlarged para-tracheal, subcarinal, and right hilar lymph nodes.

The patient continued to have persistent hypoxia and fine crackles on auscultation. Repeat chest X-rays showed persistence of bibasilar consolidation with areas of ground-glass opacities in the upper and mid zones. On day 11 of admission, a lung biopsy was performed for a more definitive diagnosis. Following the lung biopsy, the patient remained intubated due to respiratory failure and also developed acute renal failure while in the pediatric intensive care unit. On conventional ventilation, his oxygenation index quickly deteriorated to 31 despite increased positive end-expiratory pressure. He was switched to airway pressure release ventilation with fairly high settings, and use of extracorporeal membrane oxygenation (ECMO) was being considered. However, before ECMO was begun, the lung biopsy results became available (Figure 3) and the patient was immediately started on appropriate therapy.

Figure 2. One of the sections of the computed tomography scan of the patient’s chest showing bilateral opacities with irregular margins interspersed with areas showing a ground-glass appearance and interstitial thickening.

Figure 3. Lung biopsy slide with hematoxylin and eosin staining (10x magnification). Note the multiple non-caseating granulomas.
Diagnosis:

Sarcoidosis

The patient’s lung biopsy confirmed the diagnosis of sarcoidosis.

HOSPITAL COURSE

Following the completion of 5 days of methylprednisolone therapy, the patient was continued on oral steroids and weekly intramuscular injections of methotrexate. He was subsequently weaned off supplemental O2 and was discharged after a 25-day hospital stay with continued outpatient therapy for sarcoidosis. He had pulmonary function testing done at his first follow-up in the pulmonary clinic. The results were as follows: forced vital capacity (FVC) 48% predicted, forced expiratory volume in 1 second (FEV1) 40% predicted, FEV1/FVC ratio of 72%, reduced lung volumes, and increased residual volume and residual volume/total lung capacity (RV/TLC) ratio—all of which are suggestive of a mixed obstructive and restrictive defect. The patient has shown significant improvement in his chest X-ray (Figure 4) and lung function parameters (FVC 70% predicted, FEV1 60% predicted, and FEV1/FVC ratio of 76) almost 3 months after the onset of his symptoms. Clinically, he remains asymptomatic and is being continued on oral steroids and once-weekly Methotrexate therapy.

DISCUSSION

Juvenile sarcoidosis is a rare multisystem disease that has a wide spectrum of clinical features and modes of presentation. Sarcoidosis in children has no gender predominance (as opposed to adults, where its slightly more common in women), but there is a higher prevalence in African-Americans (40 per 100,000) than in whites (5 per 100,000). The mean age of onset is 10.6 years and the incidence has been estimated to be 0.22 to 0.27 per 100,000 children younger than age 15 years. The prognosis seems to be worse in younger children and in those with multisystem involvement.

For a child presenting with acute-onset respiratory symptoms and bilateral diffuse infiltrates on radiologic imaging, an infectious etiology is the likely cause in most situations. The differential diagnosis includes bacterial, viral, (rarely) fungal or mycobacterial etiologies. However, if there is no evidence of an infectious organism identified by culture, and there is a lack of response to antimicrobial therapy, then several non-infectious etiologies (diffuse alveolar hemorrhage, acute eosinophilic pneumonia, collagen vascular disorders, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, sarcoidosis, etc.) should be considered. Our patient presented with cough, shortness of breath, and diffuse pulmonary infiltrates, which then progressed to acute respiratory failure. Although there are reports of sarcoidosis presenting with acute respiratory failure in adults, this is the first pediatric case where acute respiratory failure developed during the initial presentation of sarcoidosis. Our patient was initially treated with antibiotics and antifungal therapy, but there was no response and BAL cultures remained negative. There were no eosinophils or hemosiderin-laden macrophages noted on the BAL fluid, thus ruling out acute eosinophilic pneumonia and alveolar hemorrhage syndromes, respectively. The lung biopsy results (Figure 3) gave a definitive diagnosis, with presence of multiple non-caseating granulomas and negative stains for fungal and mycobacterial organisms. Because there were no features of vasculitis, necrotizing sarcoid granulomatosis was not likely. The patient responded well to therapy with high-dose intravenous (IV) steroids initially, followed by continued maintenance anti-inflammatory therapy with oral steroids and weekly methotrexate.

Gupta et al summarized the case reports of adults with sarcoidosis presenting with acute respiratory failure during initial presentation, but such a presentation has not been reported in children. In most of these cases, lung biopsy led to the final diagnosis, although in some reports skin biopsy and mediastinoscopic lymph node biopsy also showed the characteristic granulomas of sarcoidosis. The authors also discussed the importance of a lung biopsy before steroid therapy is initiated and the fact that sarcoidosis should be considered in the differential diagnosis of acute respiratory failure of unclear etiology when other causes have been excluded.

Our patient had developed respiratory failure during the course of his hospital stay and recovered after IV steroid therapy was initiated. He had an acute respiratory distress syndrome (ARDS)-
like clinical and radiographic picture, and had also developed acute renal failure, which was believed to be pre-renal in etiology. The patient did not show evidence of sepsis and did not need inotropic support. The initial chest X-ray findings and positive Mycoplasma titers led to him being treated for community-acquired pneumonia. Because there was a lack of improvement in the clinical condition, a chest CT scan was done that showed bilateral opacities with interstitial thickening, and enlarged paratracheal, subcarinal, and right hilar lymph nodes. As BAL cultures were all negative and the patient was not showing any improvement with continued supplemental O₂, a lung biopsy was done for definitive diagnosis. The BAL CD4 to CD8 ratio of greater than 3.5 has been used in some reports as an indicator of pulmonary sarcoidosis, but it has low sensitivity (53%-59%) even though its specificity is fairly high (93%-96%). Because sarcoidosis is a disorder with polarized T-helper type 1 (Th1) immune response, our patient’s BAL immunophenotyping also showed activated T cells with equal distribution of both CD4 and CD8 T-cell types. Hypercalcemia is seen in up to 30% of cases, and an elevated angiotensin-converting enzyme (ACE) level, although not pathognomonic, is considered an important diagnostic marker for sarcoidosis.

The lung biopsy (Figure 3) revealed multiple, densely packed non-caseating, non-necrotizing (and few necrotizing) granulomas without any eosinophilic infiltration. Special staining for fungal (GMS [Grocott’s methenamine silver], PAS [periodic acid–Schiff]), mycobacterial (AFB [acid-fast bacillus], Fite), and spirochetal (Warthin-Starry) organisms was negative, and no foreign polarizable material was identified. The granulomas were composed primarily of histiocytes (CD68+, CD31+, S100 negative, CD1A negative) with admixture of CD3+ lymphocytes. Both CD4+ and CD8+ lymphocyte populations were equally represented within the granulomas. The patient’s serum ACE and calcium levels were found to be mildly elevated, further supporting the diagnosis of sarcoidosis. With the results from the lung biopsy and the patient’s overall lack of response to all other interventions, he was started on a 5-day course of methylprednisolone therapy. His chest X-rays as well as ventilatory requirements showed immediate improvement, and he was extubated after a total of 7 days of ventilatory support.

We also assessed the BAL cellular fraction in more detail. The BAL CD4+ to CD8+ lymphocyte ratio was 0.53. Immunophenotyping of BAL fluid by flow cytometry showed mature lymphocytes (30%) and a prominent population of mixed mature, infiltrating myeloid cells (66%). The gated lymphocytes were T cells with elevated expression of activation-associated marker HLA-DR. Further investigations (eye exam, renal ultrasound, echocardiogram) to evaluate for systemic involvement in relation to sarcoidosis showed no abnormalities.

CONCLUSION

This case highlights the fact that pediatric sarcoidosis can, in rare cases, present with acute respiratory symptoms and acute respiratory failure. Sarcoidosis should be considered in the differential diagnosis of a patient presenting with diffuse lung disease of unclear etiology when acute infections, hemorrhage, and fungal or mycobacterial infection have been excluded. When presenting with such fulminant onset, any delays in the diagnosis and treatment potentially could be fatal. Open lung biopsy should be considered in patients with diffuse lung disease that is unresponsive to standard therapies to make a more definitive diagnosis.

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