CLINICAL VIGNETTE

Pneumonia and cold agglutinins: A Case of Mycoplasma pneumoniae

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Case Report

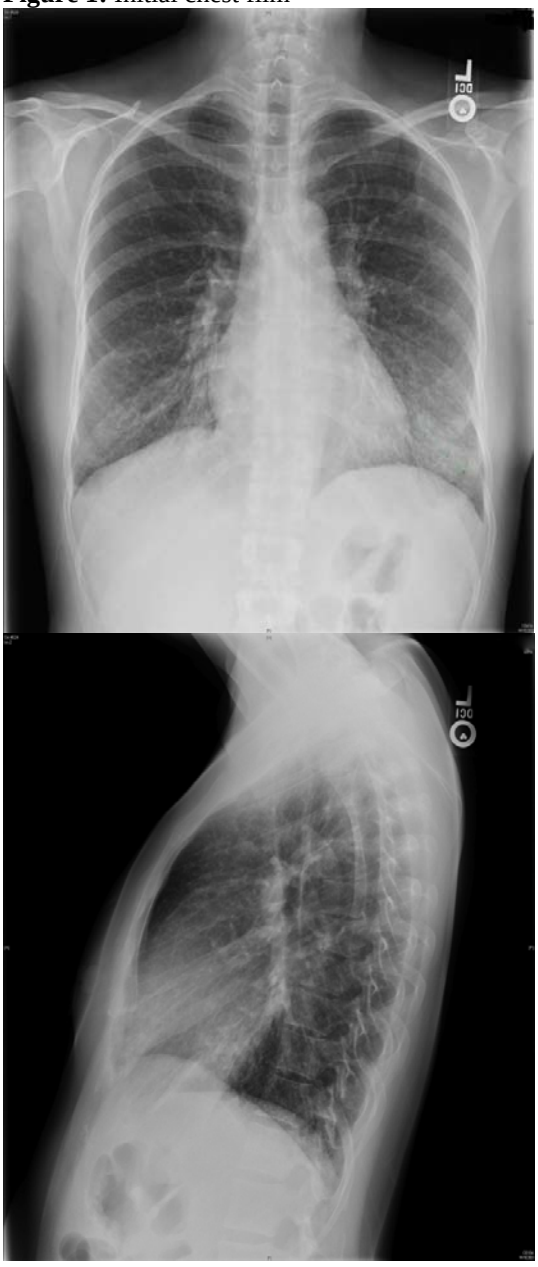
A previously healthy 46 year-old woman presented to primary care clinic with one week of cough and dyspnea on exertion. The cough was initially dry but became productive of yellow sputum two days prior to presentation. She described shortness of breath with walking only 15 feet. She also reported occasional wheezing and subjective fevers. She was found to be tachycardic and hypoxemic, prompting referral to the emergency room for further evaluation.

Her past medical history is significant for childhood asthma. She was not taking any medications or supplements. Family history was notable for pulmonary embolism in her father. She was born and raised in Los Angeles without recent travel. She denied tobacco use, alcohol consumption or recreational drug use.

Vitals upon presentation to the ED revealed temperature of 97.9 F, pulse of 115 beats per minute, blood pressure of 137/89 mmHg, respiratory rate of 20 breaths per minute, and an oxygen saturation of 92% on room air. On exam she was in no distress and sitting comfortably in bed. There was conjunctival pallor, a regular tachycardia without murmurs, and faint bibasilar rales without wheezing. The remainder of the physical exam was unremarkable.

Initial laboratory values were notable for a normocytic anemia with a hemoglobin of 6.9 g/dL. White cell count was 10.2 $x10^3$/uL with 81% neutrophils and without eosinophilia. Chest radiograph demonstrated diffuse micro-nodular opacities of both lungs with more focal left lower lobe nodular densities (Figure 1). CT angiogram of the chest was negative for pulmonary embolism, but confirmed multifocal consolidation predominantly in the right middle and left lower lobes along with innumerable centrilobular nodules on the left and bronchial wall thickening (Figure 2). She was hospitalized and started on intravenous ceftriaxone and azithromycin for community acquired pneumonia.

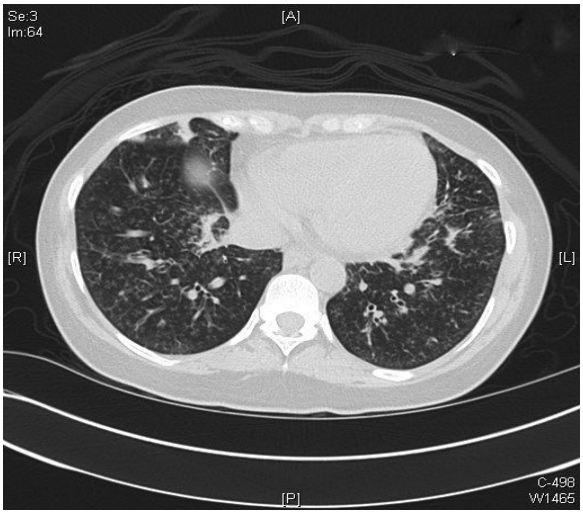
Figure 1: Initial chest film



Two units of packed red blood cells were infused with an appropriate response. Assays for cold

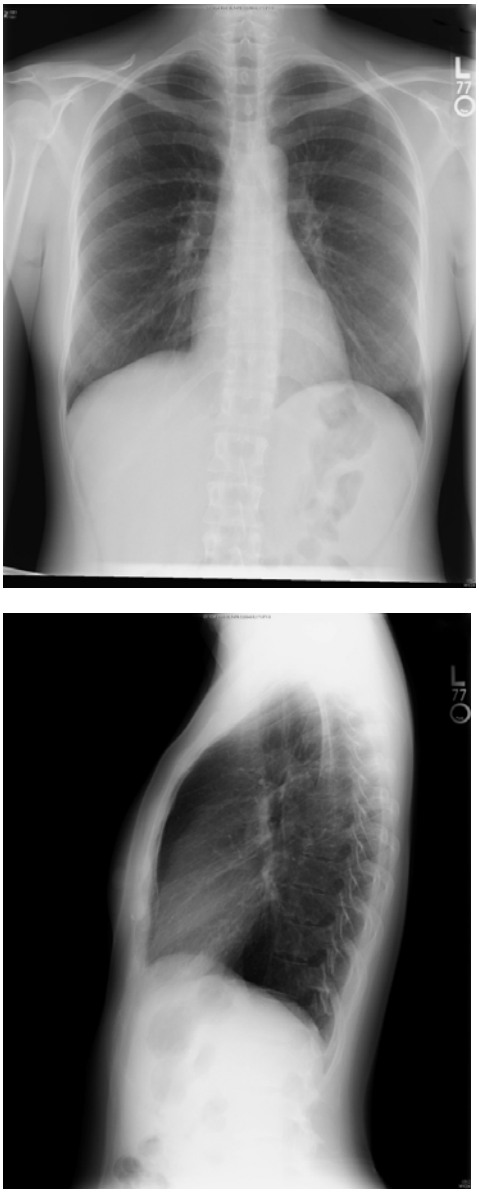
agglutinin antibodies and C3 direct antiglobulins were positive. Normal haptoglobin, LDH and bilirubin levels argued against significant hemolysis. The ferritin was 19 ng/mL with a transferrin saturation of 11% and reticulocyte index of 0.5% consistent with iron deficiency. Folate and B12 levels were normal. Further history revealed many years of menorrhagia. Multiple fibroids were noted on abdominal ultrasound and CT. Oral iron therapy was started.

Figure 2: CT angiogram of the chest



The presence of cold agglutinin antibodies raised suspicion for various pulmonary infections. Mycoplasma IgM was positive at 1.39 (reference value <0.76) and IgG was positive at 0.38 (reference value <0.09). QuantiFERON®-TB Gold was indeterminate, but three separate sputum acid-fast bacilli stains and cultures and a serum PCR for tuberculosis were negative. Blood cultures, sputum cultures, HIV, Coccidioides IgG and IgM EIA, Legionella urine antigen, EBV, Histoplasma urine antigen, and a hypersensitivity pneumonitis panel were also negative. A positive Mycobacterium avium complex culture was felt to reflect colonization. By hospital day five, her cough and dyspnea were significantly improved and antimicrobials were deescalated to azithromycin. She was discharged the following day to complete a 10-day course.

Figure 3: Repeat chest film



The patient then presented to the emergency room ten days after discharge with worsening cough, wheezing, and shortness of breath. Repeat chest radiograph demonstrated continued improvement in opacities (Figure 3). She was discharged home after nebulized bronchodilators and an oral dose of prednisone, to be continued as a taper. However, she reported persistent symptoms at a follow up clinic appointment. Peak flow measurements were decreased at 170 L/min, which again responded well to nebulized albuterol. A course of levofloxacin and an albuterol rescue inhaler were added to her prednisone taper. She continued to require daily

albuterol prompting pulmonary medicine evaluation. Inhaled mometasone/formoterol was added as controller therapy for asthma.

Discussion

The first Mycoplasma isolated in culture was bovine pleuropneumonia in the 1890's[1], and the first Mycoplasma pneumoniae was isolated from sputum in 1944[2]. The bacteria are a common cause of pneumonia internationally. It has been implicated as the cause of 25-35% of all outpatient pneumonias[3,4]. Transmission is airborne via respiratory droplets with an incubation time of one to three weeks.

Clinical mycoplasma infections occur in both the upper and lower respiratory tracts. Presenting symptoms are non-specific and include a dry or productive cough, fever, pharyngitis, headache, and malaise. Dyspnea may be present in more severe disease[5]. Fulminant cases with multi-organ involvement are unusual[4]. Risk factors for severe pneumonia include immunosuppression, hemoglobinopathy, Down's syndrome and a smoking history[6]. Immunologically mediated extrapulmonary manifestations occur in as many as 25% of patients. Central nervous system complications are the most frequent and can be fatal. These include encephalitis and aseptic meningitis with visual changes. Other complications include nonspecific gastrointestinal symptoms, Stevens-Johnson Syndrome, glomerulonephritis, polyarthritis, and hemolytic anemia[7], which may be due to the cross-reactivity between human and M. pneumonaie antigens[2].

In patients presenting with Mycoplasma pneumonia, physical examination findings are non-specific and include wheezing and rhonchi on chest auscultation. Radiographic manifestations are variable. Diffuse reticular densities in a perihilar and lower lobe distribution can be demonstrated in over 90% of cases. Unilateral disease is more common but bilateral involvement occurs in up to 20% of cases.[8] Bacterial culture remains the gold standard diagnostic test. However, specialized media is required and cultures may require up to three weeks for detectable growth. Serologic antibody titers, both complement fixation and enzyme immunoassay, have become the most common means of diagnosis. Serum and sputum PCR may also be diagnostic[2].

Cold agglutinins are commonly associated with Mycoplasma pneumonia and are present in up to 50-60% of cases[9]. However, they are not specific and have been reported with other infections including infectious mononucleosis, cytomegalovirus, Klebsiella and mycobacterial pneumonias in addition to malignancies.[10] They were first demonstrated with a case of bronchopneumonia in 1918[11]. In 1943, Maclean made the first correlation between cold agglutinins and atypical pneumonia.[12] Titers rise approximately one week after the onset of infection. Complement activation and hemolysis do not occur unless temperature drops below core body temperature[13]. Hemolysisis is thought to be mediated by antibodies against a Mycoplasma cell membrane antigen which is similar to the group I antigen on the erythrocyte cell membrane[14]. Many patients have a mild subclinical hemolysis but massive hemolytic anemia is rare[15].

Mycoplasma lacks a cell well and is therefore resistant to beta-lactam antimicrobials. Effective treatments are directed at inhibition of DNA or protein synthesis and include macrolides, fluoroquinolones and tetracyclines. Azithromycin is the most active macrolide and has a favorable side effect profile relative to erythromycin. An increased incidence of in vitro macrolide resistance has been reported. However, a recent clinical study reported zero treatment failures even in those with resistant strains[16].

Lastly, the reactivation of childhood asthma in the described case is interesting. Proinflammatory cytokines released during Mycoplasma infections have been linked to exacerbations of underlying asthma[7]. Kraft et al demonstrated that Mycoplasma nucleic acid detected by PCR can be found in airway cultures of nearly 60% of patients with chronic, stable asthma[17]. Treatment with macrolide antibiotics in these asthmatic patients with a positive Mycoplasma assay also resulted in improved pulmonary function tests.[18]

Conclusions

Mycoplasma is a common cause of atypical community acquired pneumonia. Initial symptoms, signs, and imaging studies are nonspecific and the fastidious organism is difficult to culture. A positive cold agglutinin titer provides a useful diagnostic clue and the diagnosis can be confirmed with positive serologic antibody titers or by PCR. Macrolides are an efficacious treatment for Mycoplasma and the lack of a cell wall renders beta-lactam antimicrobials ineffective. Finally, there is a developing body of

evidence suggesting a possible link between mycoplasma infection and asthma.

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