An interesting case of mycoplasma pneumonia associated multisystem involvement and diffuse alveolar hemorrhage

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A 74-year-old woman with controlled hypertension, diabetes mellitus type 2, and remote history of marginal zone B-cell lymphoma, was admitted in the summer of 2016 with abdominal pain, watery diarrhea of 1–2 days duration associated with body-aches, progressive dyspnea, and dry cough of 2–3 weeks duration. She reported unintentional weight loss of 20 pounds during this time.

She denied recent travel, sick contact, or hospitalization. She was a light smoker of 3–5 cigarettes/day. On physical exam, she was an elderly woman in mild distress, febrile (38.9°C), tachypneic (RR 22 breath/min), tachycardic (HR 110 beats/min), hypoxic with oxygen...
Laboratory results. 

| Test                     | Result             | Test                     | Result             |
|--------------------------|--------------------|--------------------------|--------------------|
| Hemoglobin (12–16 g/dL)  | 9.1                | Serum sodium             | 137                |
| Hct (42–51%)             | 28.9               | Lactic acid (0.5–1.6 mM/L) | 0.6               |
| Platelet count (150–400 K/µL) | 311               | Blood urea nitrogen     | 21                 |
| White blood cell count (4.8–10.8 K/µL) | 5.5              | Creatinine (0.5–1.5 mg/dL) | 2.2               |

3. Discussion

Mycoplasma pneumoniae (MP) infections are a worldwide cause of pneumonia affecting all age groups with variable severity. Severe mycoplasma infections are rare, with only 0.5–2% cases having a fulminant course [6].

Manifestations of MP may be multi-systemic (Table 2) [5]. Organs can be affected by one of three mechanisms: (1) direct, with bacterium present at the site of inflammation and activation of local inflammatory cytokines; (2) indirect, due to the effect of an altered immune response; or (3) vascular occlusion or impairment leading to organ dysfunction [5].

The pathogenesis of pulmonary MP includes local cytotoxic injury and poorly understood exaggerated immunological response. Autoimmune phenomena can be prominent and attributable to antigenic mimicry and direct cell activation. Cold agglutinins to the I-antigen of human red blood cells are a common finding [7]. Adhesion molecules P30 and P1 are found in an attachment organelle of the pathogen for cytoadherence [2]. A potential exotoxin, an ADP-ribosyltransferase in the pathogen's genome called community-acquired respiratory distress syndrome (CARDS) toxin, causes vacuolation and ciliostasis in cultured host cells [2]. Mycoplasma-infected type II pneumocytes show higher levels of interleukin (IL)-8, tumor necrosis factor-α and IL-1-β mRNA production, resulting in increased cytokine levels and recruitment of lymphocytes and inflammatory cells [8,9]. Cytokines can result in diffuse alveolar epithelial membrane injury leading to DAH; this has been demonstrated in stem cell transplant patients [10]. Mycoplasma-induced IgM cold agglutinins cross-react with I antigen containing erythrocyte glycoproteins. In the bronchial epithelium, the I antigen is contained in long-chain sialo-oligosaccharides that can serve as receptors for MP [2]. Disruption and cytokotoxicity of lung tissue leading to DAH can be produced by the CARDS toxin, hydrogen peroxide, and superoxide, causing injury to epithelial cells, and damaged red blood cells due to anti-I cross-reactivity may extravasate into the alveolar space [2,6,8–10].

Causative factors for DAH are dependent on the patient’s immune status and can be classified as either non-infective or infective. In immunocompromised patients, infective agents of DAH include cytomegalovirus, adenovirus, invasive aspergillosis, Mycoplasma, Legionella, and Strongyloides [11]. In immunocompetent patients, influenza A (H1N1), dengue, leptospirosis, malaria, and Staphylococcus aureus infection have been associated with DAH [11]. Severe mycoplasma with MP-associated DAH is rare, with only two cases identified in the English literature [3,4].

Diagnosis is based on findings of hemoptysis, anemia, diffuse or worsening infiltrates, and hypoxic respiratory failure. Bronchoscopy showing hemorrhagic sequential lavage and hemosiderin-laden macrophages support the diagnosis. The latter is usually found after 48–72 hours of hemoptysis [12].

The diagnosis of MP infection is based on serology, particularly IgM detection by ELISA. Sensitivity of IgM assays increases with the duration of symptoms, approaching more than 70% after 15 days of symptoms [13]. The positive predictive value for most of the test ranges from 60 to 80% [13]. Cross-reactivity with Epstein Barr Virus (EBV) is common. Cold agglutinins help to confirm the diagnosis, they are increased in 50–60% of patients, but may occur in EBV,
cytomegalovirus, or Klebsiella infection. Anti-I-specific IgM-cold-agglutinin is more specific for diagnosis [14]. PCR and serological analyses could be good screening tests for the reliable and accurate diagnosis of MP [2]. Bacterial culture is time-consuming and not readily available [2].

The Japanese Respiratory Society scoring system for atypical pneumonias is able to diagnose MP pneumonia with 88.7% sensitivity and 77.5% specificity [15]. The presence of more than four out of six of the following parameters provides high suspicion for MP; age <60 years, absence of or minor underlying diseases, stubborn cough, positive findings in chest auscultation, absence of sputum, or identifiable etiological agent by rapid diagnostic testing and serum white blood cell count <10^9/L [15]. Our patient exhibited five parameters, and in addition elevated IgM and high anti-I-specific cold agglutinin levels. Other causes of DAH were ruled out by appropriate serological tests.

It is imperative that an etiological diagnosis for DAH be established to initiate appropriate therapy. In patients with MP infection, macrolides are the drug of choice in adults and children; however, there are growing concerns regarding the development of resistance [1]. Acquired mutations on the ribosomal macrolide target are the only resistance mechanism described [2]. Resistance in Europe and USA may be in up to a quarter of patients, whereas resistance in Japan and China may be approaching more than 90% [16]. Therapeutic alternatives include fluoroquinolones, primarily levofloxacin, and tetracyclines [17]. The management of DAH is supportive. Corticosteroid and immunosuppressive therapies are controversial [11]. Daily or alternate day plasmapheresis may be considered according to the guidelines of the American Society for...
Apheresis in patients with DAH presenting with severe hypoxemic respiratory failure [18,19].

4. Conclusions

Diffuse alveolar hemorrhage in a patient with CAP should raise suspicion for severe MP infection. Cases may be missed due to low suspicion. The Japanese Respiratory Society Scoring System may prove useful in these scenarios. Mycoplasma pneumonia should be included as part of the differential diagnosis in patients with CAP and multi-organ involvement. Plasmapheresis may be lifesaving and should be considered for severe DAH associated with infectious causes. Sudden death can occur in MP infection, likely due to thrombotic or cardiac complications.

Conflicts of interest

The authors report no conflicts of interest.

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