Interval Development of Multiple Sub-Segmental Pulmonary Embolism in *Mycoplasma Pneumoniae* Bronchiolitis and Pneumonia

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Abstract

Introduction: Cases of pulmonary embolism (PE) concurrent with *Mycoplasma pneumoniae* infection are rare in the medical literature. We describe a patient with *M. pneumoniae* bronchiolitis and pneumonia who developed multiple right-sided, sub-segmental PE.

Case Description: A 54-year-old man presented following one week of respiratory and constitutional symptoms. He was admitted for respiratory distress and started on ceftriaxone, azithromycin, and oseltamivir. Because of a lack of clinical improvement, antibiotics were escalated to vancomycin and piperacillin-tazobactam. *M. pneumoniae* IgM and IgG serologies returned positive, and antibiotics were narrowed to azithromycin, with clinical improvement and gradual decrease in supplemental oxygen requirement. One week into the hospitalization, the patient abruptly developed an increased oxygen requirement. Computed tomography angiography (CTA) of the chest found stable *M. pneumoniae* bronchiolitis and pneumonia and the interval development of multiple right-sided, sub-segmental PE. He was treated with unfractionated and then low-molecular-weight heparin as a bridge to warfarin, azithromycin, and a prednisone taper. In the outpatient setting, repeat CTA revealed resolution of *M. pneumoniae* infection and PE.

Discussion: Although the mechanism and association are unclear, other case reports have proposed that *M. pneumoniae* infection promotes hypercoagulability or a prothrombotic state, predisposing patients to thromboembolism. In a patient with *M. pneumoniae* infection who develops sudden respiratory distress or failure despite appropriate treatment, clinicians should have a high suspicion for PE, and a CTA should be considered as part of further evaluation.

Introduction

Mycoplasma pneumoniae is one of thirteen *Mycoplasma* species isolated from humans and less commonly causes lower respiratory tract infections, of which atypical pneumonia occurs at higher rates (1). These lower respiratory tract infections have been reported to present similarly to other disease processes such as asthma and pulmonary embolism (PE) (2, 3). *M. pneumoniae* pneumonia typically has a benign course with low mortality. A study by von Baum *et al.* found a mortality of 0.7% in

patients with *M. pneumoniae* pneumonia, with the deaths occurring in hospitalized patients (4). Despite this low mortality, rare complications may contribute to morbidity and mortality, although to what degree, if any, is unclear. A case report in the medical literature describes a PE and a hypercoagulable state associated with *M. pneumoniae* pneumonia in an adult during the peri-infectious period (5). We present a case with radiographic evidence of the interval development of multiple segmental PE in a patient with *M. pneumoniae* bronchiolitis and pneumonia.

Case Description

A 54-year-old man with a 15-pack-year smoking history, positive purified protein derivative treated with isoniazid, occupational exposures including asbestos and dust, and a current history of ethanol abuse presented to the emergency department with a one-week history of a productive cough with yellow sputum, weakness, shortness of breath, and dyspnea on exertion. He also noticed diffuse papular cutaneous lesions over his back.

In the emergency department, he was hypoxic with a need for supplemental oxygen. Cardiopulmonary examination was unremarkable. Initial laboratory studies including complete blood count, chemistry panel, and hepatic function panel were notable for a leukocytosis of 13.6 k/ μ L with a neutrophilia of 83%, aspartate transaminase of 108 units/L, alanine transaminase of 152 units/L, alkaline phosphatase of 175 units/L, and total bilirubin of 1.5 mg/dL, and creatine kinase of 563 units/L. Conventional chest radiograph (Figure 1) showed a left lower lobe infiltrate.

Figure 1. Conventional chest radiograph on day zero of the hospitalization. The images show a left lower lobe infiltrate.

The patient was admitted to the hospital and started on ceftriaxone and azithromycin for community-acquired pneumonia as well as oseltamivir over concerns for influenza.

During the initial hospitalization, the patient required supplemental oxygen for hypoxia with a rapid increase in fractional inspired oxygen (F_iO_2) to maintain oxygen saturation above 90%. Because of a lack of clinical improvement, antibiotics were broadened to include vancomycin and piperacillin-tazobactam. Since he continued to require a F_iO_2 of 60% on day four of the hospitalization, additional workup for atypical bacterial, viral, and fungal pathogens were performed after consultation with pulmonology. Acid-fast bacillus cultures and stains were negative. Sputum cultures were not obtained. An arterial blood gas prior to evaluation by Pulmonology found a pH of 7.42, partial pressure of carbon dioxide of 38 mmHg, partial pressure of oxygen of 86 mmHg, HCO_3 of 24 mmol/L, and F_iO_2 of 95%. Computed tomography (CT) of the chest (Figure 2) showed extensive bronchiolitis with focal areas of consolidation involving bilateral lower lobes.

Figure 2. Computed tomography of the chest on day four of the hospitalization. The image shows an extensive bronchiolitis with focal areas of consolidation involving bilateral lower lobes.

Oseltamivir was discontinued after the respiratory viral panel returned negative. Broad spectrum antibiotics were narrowed to azithromycin after *M. pneumoniae* IgM and IgG serologies returned positive. His oxygen requirement gradually improved over the next two days, and he was transitioned to nasal cannula.

On day seven of his hospitalization, the patient suddenly developed moderate respiratory distress with an increase in oxygen requirement. CT angiography (CTA) of

the chest (Figure 3) done at this juncture showed unchanged parenchymal findings with interval development of multiple sub-segmental pulmonary emboli in the right lung.

Figure 3. Computed tomography angiography of the chest on day five of the hospitalization. The images show unchanged parenchymal findings with interval development of multiple sub-segmental pulmonary emboli in the right lung (see white arrows in Figure 3A).

Doppler ultrasound found no evidence of deep venous thrombosis (DVT) in both lower extremities. He was subsequently started on therapeutic anticoagulation with unfractionated heparin and then low-molecular-weight heparin as a bridge to warfarin. The patient subsequently improved on a 14-day course of azithromycin 500 mg orally once daily and 3-month tapered course of prednisone 60 mg orally once daily for *M. pneumoniae* infection, a 3-month course of warfarin for the PE, and supplemental oxygen. During follow-up in the outpatient setting, CTA of the chest showed the infection and PE to have resolved, and all therapies related to the infection and PE were discontinued.

Discussion

We herein describe a case of *M. pneumoniae* bronchiolitis and pneumonia complicated by right-sided PE. The reported occurrences of venous thromboembolism (VTE) during *M. pneumoniae* infection are limited to case reports. In our review of the literature, we found one case of *M. pneumoniae* infection associated with PE in the adult population. Ascer *et al.* (5) presented the case of a 28-year-old male with right-sided pneumonia and right-sided PE who was found to have antiphospholipid antibodies. For the PE, this patient was successfully treated with recombinant tissue-type and plasminogen activator and heparin and was discharged with hydroxychloroquine sulfate, aspirin, and warfarin. However, Ascer did not publish additional follow up for this seemingly prothrombotic state. In a case without PE, Senda *et al.* (6) reported on a 21-year-old patient with a left middle cerebral artery embolus and DVT in bilateral femoral veins in the setting of a *M. pneumoniae* infection. This patient had a transient increase in prothrombin time, partial thromboplastin time, fibrin/fibrinogen degradation products, thrombin-antithrombin III-complex, antiphospholipid antibodies, and IgM anticardiolipin antibodies and decrease in protein C activity.

The pediatric medical literature has additional case reports linking *M. pneumoniae* to PE. Brown *et al.* (7) described a 6-year-old male child with *M. pneumoniae* pneumonia, right-sided ileofemoral thrombosis, and right-sided PE found to have anticardiolipin IgG and IgM antibodies, lupus anticoagulant, and acquired activated protein C resistance. This prothrombotic state subsequently resolved after treatment of the infection with antibiotics and the PE with unfractionated heparin and then dalteparin. In another case report, during workup for a 13-year-old male child with right-sided PE in the setting of a left lower lobe *M. pneumoniae* pneumonia, Graw-Panzer *et al.* (8) found lupus anticoagulant, anticardiolipin IgG and IgM antibodies, and an underlying protein S deficiency. The transient prothrombotic markers returned to normal levels during subsequent follow-up for his acute illness.

M. pneumoniae pulmonary infections have been reported in the pediatric medical literature to be associated with an underlying hypercoagulability. Creagh *et al.* (9) reported on a left femoral vein thrombosis in a 10-year-old female with *M. pneumoniae* pneumonia who was found to have type I familial antithrombin III deficiency. In another case report of two children describing splenic infarcts associated with *M. pneumoniae* pneumonia, Witmer *et al.* (10) found elevated D-dimer, lupus anticoagulant, and elevated anticardiolipin and β 2-glycoprotein antibodies that resolved following successful treatment of the infection with antibiotics and a three-month course of anticoagulation and, in one patient, an additional course of aspirin (10). No specific etiology was found for the infarctions, but Witmer *et al.* attributed the infarctions to possible thrombosis. Other case reports in the pediatric literature that found antiphospholipid antibodies include a patient with cardiac thrombus and internal carotid artery occlusion (11, 12). However, in their report of right popliteal artery thrombosis in a 5-year-old male child with *M. pneumoniae* pneumonia and right popliteal artery thrombosis, Joo *et al.* (13) did not find abnormalities in their limited hypercoagulability workup.

Our lack of hypercoagulability workup limits comparison with the available medical literature. We did not perform a hypercoagulability workup because the patient did not meet any Wells criteria and did not have a family history of hypercoagulability. Based on the available case reports, the underlying pathophysiology can be inferred to be related to a transient formation of antiphospholipid antibodies during a *M. pneumoniae* infection. Additionally, the thromboembolism can be expected to occur within a short period of time following the onset of symptoms. The rate that hypercoagulability occurs in infected patients and the practical clinical relevance of such a prothrombotic state without or without an inherited or congenital deficiency are unknown at this time. These questions would benefit from further investigation.

An alternative interpretation is a preexisting hypercoagulability may predispose patients to *M. pneumoniae* infection, which can exacerbate the hypercoagulability, further increasing the risk of VTE. This interpretation may be relevant for the patients of Graw-Panzer *et al.* (8) and Creagh *et al.* (9) who had underlying hypercoagulable conditions and subsequently suffered *M. pneumoniae* infection and then developed VTE. The

Worcester Venous Thromboembolism study found an association between infection and VTE, and Rosendaal's review of the literature found an association between hypercoagulability and increased risk of thrombosis (14-16). With the available case reports and epidemiological studies, this alternative interpretation has not been elucidated.

In this report, we described the interval development of PE in a patient with *M. pneumoniae* bronchiolitis and pneumonia. The mechanism for the hypercoagulability during *M. pneumoniae* infection is unclear. A CTA of the chest should be obtained if a patient with *M. pneumoniae* infection fails to show clinical improvement or suddenly develops clinical worsening of his or her respiratory status, so as to exclude PE. However, clinicians should take into account that *Mycoplasma pneumoniae* may present with the symptoms of PE (3).

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