Case Report
Early recognition and management of pulmonary embolism related to mycoplasma pneumoniae infections in children: two case reports and literature review

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Abstract: Objective: To explore the clinical characteristics and risk factors of mycoplasma pneumoniae (MP) infections complicated by pulmonary embolism in children. Methods: We report two cases of MP infections complicated by pulmonary embolism (PE). We also reviewed all reports of pulmonary emboli resulting from MP infections in the past fifteen years. Results: Two children with PE were enrolled: a 9-year-old girl presented with bloody effusion and hemoptysis and a 7-year-old boy with chest pain and hemoptysis. We found 7 case reports of MP infection with PE. Nine cases aged from 6 to 13 years were reported in the past 15 years, of which 7 cases were male and 2 female. Five patients had chest pain, three had hemoptysis, and two had bloody pleural effusions. Four patients had emboli in the veins of their lower limbs. The D-dimer levels were increased significantly in all patients. Anti-cardiolipin antibodies of seven cases were positive. Conclusion: MP infection may lead to a hyper-coagulative state and potential to thrombosis because of autoantibodies especially antiphospholipid antibodies. Early diagnosis with anti-coagulation and thrombolysis treatment actively is the key to a better prognosis.

Keywords: Mycoplasma, pneumonia, embolism, antiphospholipid antibodies, thrombolysis

For children, mycoplasma pneumonia (MP) is a common cause of community-acquired pneumonia but pulmonary embolism (PE) is uncommon. There are few case reports associating MP infection with the development of pulmonary embolism. Because of its vague symptoms and relative rarity, pediatric PE remains a clinical problem for clinicians [1]. In this article, we report two cases of MP infection complicated by pulmonary embolization diagnosed in our hospital. We also reviewed all reports of pulmonary emboli from MP infections in the past fifteen years. The aim is to explore the clinical characteristics and risk factors of PE associated with MP infection.

Case report
Case 1
A previously healthy 9-year-old girl presented with a history of 2 weeks of fever and cough. Prior to admission, the chest radiograph revealed right middle and lower lobe consolidation with effusion. She received intravenous azithromycin for two courses of treatment but still had fever and cough. Upon admission she was in moderate respiratory distress with a respiratory rate of 42 breaths/minute. Pulse oximetry measurements were 95% under oxygenation by nasal catheter. Upon chest examination she had decreased bronchial breath sounds, crackles in the right lung field and dullness to percussion. Her initial laboratory tests showed the following: hemoglobin 10.4 g/dL, white cell count 15.35×10^9/L, platelet count 200×10^9/L, and CRP of 22 mg/L. MP-specific immunoglobulin (Ig) M and IgG levels were elevated by ELISA (anti-Mycoplasma pneumoniae antibody test kit, SERODIA-MYCO II). Sputum viral antigen detection and bacterial cultures were negative, and a tuberculin skin test (PPD) was non-reactive. The anti-nuclear antibodies
test was negative. A chest ultrasound revealed a persisting pleural effusion. A thoracentesis was performed for three times. The pleural effusion was dark red with pH 7.38; white cell count, 140,000/mm$^3$; glucose, 1.87 mmol/l; protein, 30.4 g/l; and lactate dehydrogenase, 2100 U/L. The patient received intravenous piperacillin and vancomycin for possible bacterial infection and methylprednisolone for anti-inflammation. On day 5 of her admission to our hospital, her temperature normalized but she presented with hemoptysis. On day 9, a bronchoscopy examination showed there was bloody fluid in the lumen of the right lower branch. On day 14 she had multi-detector CT pulmonary angiography (CTA). The CTA showed pulmonary emboli in branches of the right lower pulmonary artery and an encapsulated hydropneumothorax (Figure 1A). D-dimer levels were elevated to 9.96 mg/L. She was given intravenous heparin to maintain activated partial thromboplastin time twice that of the control; this subsequently was changed to warfarin to maintain the international normalized ratio (INR) between 2 and 3 for 3 months. CTA showed that the thrombus resolved within three months.

Case 2

A 7-year-old boy was admitted to our hospital with a history of fever and cough for 18 days and hemorrhage for 1 day. Upon admission his respiratory rate was 42 breaths/minute, and his temperature was 39.2 C. His pulse oximetry measurement was 95%. Upon chest examination, he had decreased bronchial breath sounds in the left lung field. His initial laboratory tests showed the following: white cell count $8.32 \times 10^9$/L, hemoglobin 11.1 g/dL, platelet count $412 \times 10^9$/L, and CRP 22 mg/L. His chest radiography showed left lower lobe consolidation with effusion. MP-specific immunoglobulin M was positive. He received intravenous azithromycin for the MP infection and methylprednisolone for inflammation. He had chest pain and was short of breath four days prior to admission to our hospital. He received intravenous cefuroxime and gamma globulin. Two days prior to admission to our hospital his chest pain and cough were relieved. However he had hemoptysis the day before so he was transferred to our hospital. D-dimer levels were elevated to 9 mg/L. A CTA showed pulmonary emboli in the distal branches of the left lower pulmonary artery (Figure 1B). He had Wolff Parkinson White syndrome and a small amount of pericardial effusion. His pleural effusion had resolved. He had a second course of intravenous azithromycin. On day 2 of admission to our hospital, his temperature decreased to a normal temperature. He was given intravenous heparin, which was later replaced by oral warfarin for 3 months. The CTA showed that the thrombus resolved, and the range of lung consolidation was reduced three months later. The two cases had no significant family history, specifically anything suggesting thromboembolic disease, or tuberculosis contact. Other causes of thrombophilia such as protein C deficiency, anti-thrombin deficiency, elevated level of factor VIII clotting activity, dysfibrinogenemia, and hyperhomocysteinemia were excluded.

Literature review and discussion

By searching the China Hospital Knowledge Database on the China National Knowledge
### Table 1. The clinical features of the laboratory results and therapy of nine cases PE

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/sex</th>
<th>Symptoms Short of breath</th>
<th>Chest pain</th>
<th>Hemoptysis</th>
<th>Symptoms Pleural effusion</th>
<th>D-dimer (mg/L)</th>
<th>Anti-phospholipid antibodies</th>
<th>Protein C/S activity</th>
<th>Imagology</th>
<th>Time of PE</th>
<th>Other embolism</th>
<th>Therapy</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Six/M</td>
<td>+ (at the third week)</td>
<td>-</td>
<td>-</td>
<td>As mall amount of pleural effusion</td>
<td>Unknown</td>
<td>Anti-cardiolipin-antibody and lupus anticoagulant positive</td>
<td>C decreased</td>
<td>CTA: a small thrombus in the right pulmonary artery</td>
<td>The third week</td>
<td>The superficial femoral vein</td>
<td>Heparin and orally anticoagulated</td>
<td>2007, the United Kingdom [2]</td>
</tr>
<tr>
<td>2</td>
<td>Thirteen/M</td>
<td>+</td>
<td>-</td>
<td>Uncomplicated effusion</td>
<td>&gt;55.8</td>
<td>Anti-cardiolipin antibody and lupus anticoagulant positive</td>
<td>C normal, S decreased to 20%</td>
<td>CTA: pulmonary emboli in the main and distal branches of the right pulmonary artery</td>
<td>The third week</td>
<td>The left popliteal vein</td>
<td>Warfarin for 7 months</td>
<td>2009, America [3]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Six/M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Bloody effusion</td>
<td>14.81</td>
<td>Anti-cardiolipin antibody positive</td>
<td>C decreased to 60%</td>
<td>CTA: the branch of left lower bronchial artery partially obstructed</td>
<td>The third week</td>
<td>Two separated thrombi in deep veins</td>
<td>Warfarin for 5 months</td>
<td>2012, China [4]</td>
</tr>
<tr>
<td>4</td>
<td>Twelve/F</td>
<td>Fever gone with paradoxical tachypnea</td>
<td>+</td>
<td>-</td>
<td>Pleurisy</td>
<td>44.9</td>
<td>Anti-cardiolipin antibody positive</td>
<td>Undetected</td>
<td>Lung ventilation perfusion imaging: segmental perfusion defect in the left lung</td>
<td>The second week</td>
<td>Left lateral iliac artery, femoral vein and great saphenous vein</td>
<td>Warfarin for six months</td>
<td>2013, China [5]</td>
</tr>
<tr>
<td>5</td>
<td>Six/M</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>Small amount</td>
<td>5.25</td>
<td>Positive</td>
<td>C decreased to 55%</td>
<td>CTA: the right pulmonary artery and the branch of left lower bronchial artery partially obstructed</td>
<td>The third week</td>
<td>-</td>
<td>Warfarin for seven months</td>
<td>2014, China [6]</td>
</tr>
<tr>
<td>6</td>
<td>Nine/M</td>
<td>Fever gone with paradoxical tachypnea</td>
<td>+</td>
<td>+</td>
<td>Small amount</td>
<td>8.9</td>
<td>Anti-cardiolipin-β2GI antibody positive</td>
<td>C normal</td>
<td>CTA: thrombus in the right pulmonary artery</td>
<td>The fourth week</td>
<td>-</td>
<td>Warfarin for three months</td>
<td>2015, China [7]</td>
</tr>
<tr>
<td>7</td>
<td>Seven/M</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Small amount</td>
<td>4.38</td>
<td>Anti-cardiolipin β2GI antibody and lupus anticoagulant positive</td>
<td>C normal</td>
<td>CTA: thrombus in double lower pulmonary arteries</td>
<td>The second week</td>
<td>-</td>
<td>Warfarin for 3 months</td>
<td>2015, China [8]</td>
</tr>
<tr>
<td>8</td>
<td>Nine/F</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>Bloody effusion</td>
<td>9.96</td>
<td>Undetected</td>
<td>Undetected</td>
<td>CTA: thrombus in the right lower pulmonary artery</td>
<td>The fourth week</td>
<td>-</td>
<td>Warfarin for 3 months</td>
<td>2016, China</td>
</tr>
<tr>
<td>9</td>
<td>Seven/M</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Small amount</td>
<td>9.20</td>
<td>Undetected</td>
<td>Undetected</td>
<td>CTA: thrombus in distal branches of the left lower pulmonary artery</td>
<td>The third week</td>
<td>-</td>
<td>Warfarin for 3 months</td>
<td>2016, China</td>
</tr>
</tbody>
</table>

Notes: + representative positive, - representative negative, M representative male, F representative female, β2GI anti representative β2 glycoprotein I, CTA representative CT pulmonary angiography.
Pulmonary embolism related to mycoplasma pneumoniae infections

Table 2. Positive clinical features and examination results of nine cases MP

<table>
<thead>
<tr>
<th>Short of breath</th>
<th>Chest pain</th>
<th>Hemoptysis</th>
<th>Bloody pleural effusion</th>
<th>D-dimer increased</th>
<th>Anti-phospholipid antibodies positive</th>
<th>Protein C/S activity decreased</th>
<th>Other embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% (9/9)</td>
<td>56% (5/9)</td>
<td>33% (3/9)</td>
<td>22% (2/9)</td>
<td>100% (9/9)</td>
<td>100% (7/7)</td>
<td>67% (4/6)</td>
<td>44% (4/9)</td>
</tr>
</tbody>
</table>

Infrastructure Web (CNKI-CHKD) and PubMed between 2002 and 2017, we found 7 case reports of MP infection with PE. We retrospectively analyzed symptoms, signs, laboratory results, CTA results, and follow-up examinations of the nine patients (Table 1). The male to female ratio was 7:2. The age of these patients ranged from six to thirteen years, with an average of 8.3 years. All the patients had fever, cough and shortness of breath. Five patients had chest pain, three with hemoptysis, and two had bloody pleural effusions. Four patients had emboli in the veins of their lower limbs. The D-dimer levels were increased significantly in all children. Anti-cardiolipin antibodies of seven cases were positive, three cases had low protein C activity, and one case had low protein S activity (Table 2).

MP has been known to cause a wide variety of extra-pulmonary diseases with unknown pathomechanisms. They can be classified according to the three possible pathomechanisms: (1) a direct type (2) an indirect type (3) a vascular occlusion type. The incidence of PE due to MP infection is very low. We only found 7 case reports of MP infection with PE in the medical literature. Some patients may have been misdiagnosed because of their vague or subtle symptoms that mimic other pulmonary diseases. Paul G reported that the prevalence of PE among pediatric patients may be higher than previously reported with increased use of advanced imaging studies such as pulmonary CT angiography [1]. Kritsaneepaiboon and Victoria reported PE prevalence in children who underwent CTA for clinically suspected PE ranged from 14% to 15.5% in recent articles [9].

The incidence of PE is higher in boys than in girls. All the patients had refractory MP pneumonia. They are primary and middle school students. Classically, PE in children presents with pleuritic chest pain, hemoptysis, and tachypnea. Of note, tachypnea is an important indicator of PE in all pediatric patients. Those patients with paradoxical tachypnea should be suspected of PE with fever gone. If a patient had bloody pleural effusion or hemoptysis, CTA should be detected as soon as possible.

MP can lead to systemic hypercoagulable state, which is a consequence of immune modulation through the function of chemical mediators such as activated complements and fibrin D-dimer [10, 11]. The level of D-dimer was increased significantly for the nine patients. D-dimer is a sensitive but non-specific test for PE because many infectious, neoplastic, and inflammatory causes can also result in its elevation.

MP infection can cause thrombosis in many parts of the body including the lower limb veins, internal carotid artery, cerebral artery, cardiopulmonary artery, etc. The mechanism by which mycoplasma infections can cause thrombosis may be multifactorial including the development of autoantibodies. Anti-phospholipid antibodies (aPL), including anti-cardiolipin, anti-β2-glycoprotein I antibody and lupus anticoagulant, are produced in several types of infections. Anti-cardiolipin antibody is thought to be a kind of autoantibody, targeting for the structure of cardiolipin on the surface of platelet and vessel endothelial cells. Once injured, endothelial cells would express pro-coagulant and anti-fibrinolytic components, such as vWF, TXA3, P-selectin, and PAI-1 [5]. Anti-cardiolipin antibody was increased significantly more in patients with MP infection compared to patients with other infections [12]. aPL were positive particularly in patients with severe MP infection and in patients with a high titer of cold hemagglutinins [13]. Among patients who had lupus anticoagulant and/or anti-β2-glycoprotein antibodies, thrombosis was more common in those with IgG than in those with IgM antibodies and more common in those with high-titer antibodies [14]. However, aPL was not necessary for thrombotic events following MP infection. Kalicki B reported that a 14-year-old boy, with absence of the inferior vena cava, had a deep venous thrombosis with MP serum antibodies and negative anti-cardiolipin serum antibodies [15].

Anti-phospholipid antibodies can inhibit endogenous anticoagulants including protein C, protein S, anti-thrombin, and annexin A5 [16]. Recent studies showed that protein C resistance was associated with lupus anticoagu-
lants and β2GPI [17]. Lecompte concluded that decreased sensitivity of thrombin activity to activated protein C, taking into account its modulation by the genuine anticoagulant effect of aPL, was associated with an increased risk of thrombosis in aPL-positive patients [18].

Treatment options for pediatric PE include anticoagulation therapy, thrombolysis, and surgical or interventional thrombectomy. For a patient in hemodynamically stable condition, anticoagulation therapy should be instituted to prevent thrombus extension and late development of complications [1]. All patients were treated with oral anti-coagulants such as warfarin for three to seven months. The thrombus was dissolved and the prognosis was well.

Conclusion

We should be aware of the risk of PE for those children with lobar pneumonia caused by MP, particularly in those with the following characteristics: 1) A condition showing no improvement or clinical worsening with standard therapy, 2) Presence of paradoxical tachypnea in the absence of fever, or 3) Presence of bloody effusion or hemoptyis. We should examine the D-dimer, the activity of protein C/S, and the titer for anti-cardiolipin antibody. If suspicious of a PE, a CTA should be obtained as soon as possible.

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Disclosure of conflict of interest

None.

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