Pulmonary embolism triggered by cold agglutinin syndrome in mycoplasma pneumoniae pneumonia

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Abstract

Mycoplasma (M.) pneumoniae is a common pathogen causing respiratory infections in children. Pulmonary embolism is a rare complication that may be life-threatening if not diagnosed early and treated promptly. Here, we report the case of an 11-year-old patient with pulmonary embolism associated with M. pneumoniae pneumonia. The patient developed uncorrectable hypoxemia and received venovenous extracorporeal membrane oxygenation treatment. Although the mechanism of thrombosis after M. pneumoniae infection remains unknown, an increase in the cold agglutinin titer indicates that cold agglutinin syndrome might be the mechanism of this pathological change. We thought that patients who have positive cold agglutinin after M. pneumoniae infection should be monitored for the possibility of thrombosis formation.

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Key words: Mycoplasma pneumoniae; pulmonary embolism; cold agglutinin syndrome

To the Editor

Mycoplasma (M.) pneumoniae is a common pathogen causing respiratory infections in children. Pulmonary embolism is a rare complication that may be life-threatening if not diagnosed early and treated promptly. Here, we report the case of an 11-year-old patient with pulmonary embolism associated with M. pneumoniae pneumonia. The patient developed uncorrectable hypoxemia and received venovenous extracorporeal membrane oxygenation treatment. Although the mechanism of thrombosis after M. pneumoniae infection remains unknown, an increase in the cold agglutinin titer indicates that cold agglutinin syndrome might be the mechanism of this pathological change. We thought that patients who have positive cold agglutinin after M. pneumoniae infection should be monitored for the possibility of thrombosis formation.

Introduction

Mycoplasma (M.) pneumoniae is responsible for approximately 40% of community-acquired pneumonia cases in children aged $>$ 5 years, and approximately 20% of infections are asymptomatic. A rare complication is a pulmonary embolism, which may be life-threatening if not diagnosed early and treated promptly. The mechanism is unclear, but includes autoimmune or cytokine-mediated vasculitis, immune dysregulation or induction of a procoagulant activity-mediated hypercoagulable state, a decline in anticoagulant activity, and the formation of antiphospholipid antibodies.[1] Most cases are treated conservatively, and there are few reports of the use of extracorporeal membrane oxygenation (ECMO). Here, we report a case of M. pneumonia with persistent hypoxemia that was treated with venovenous (VV) ECMO. Cold agglutinin syndrome and pulmonary infarction were observed during treatment. Our study shows that the relationship between cold agglutinin syndrome and mycoplasma infection or its impact on ECMO treatment (including the use of blood products) is worth exploring further.

Case Presentation

A previously healthy 11-year-old Chinese boy had a history of 10 days of nonproductive cough, fever, and half days of dyspnea. After 6 days of intravenous antibiotics (Azithromycin and Cefmetazole sodium) in the outpatient clinic, he developed dyspnea, his C-reactive protein level was raised to 68.36 mg/L. The patient was hospitalized because of cyanosis aggravation. On admission, the patient was found to be using his accessory muscles with pulse oximetry 90% under non-invasive ventilation (FiO2 50% and 30 L/min oxygen flow). Chest examination revealed decreased air entry, dullness to percussion, and increased vocal fremitus over the right lung field, with normal breath sounds over the left. Throat swabs showed M. pneumoniae DNA positivity. Chest computed tomography (CT) showed bilateral infiltrates, partial consolidation mainly in the lower lobes, and pleural effusion on the right side. There was no significant family history or tuberculosis contact, and specifically, no evidence of thromboembolic disease.

The patient received intravenous levofloxacin and intravenous methylprednisolone (2 mg/kg, q12h). On the second day of admission, the patient suffered a progressive exacerbation of dyspnea; he received two consecutive bedside bronchoscopy treatment, and formation of bronchial casts could be seen on both sides of the tracheobronchial tree. Tests of bronchoalveolar lavage fluid showed positive M. pneumoniae DNA. However, his respiratory status contributed to worsen, oxygen saturation could not be maintained with mechanical ventilation; therefore, he received VV ECMO. Heparin was used as an anticoagulant during ECMO treatment. On day four of admission, blood tests showed that the red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) could not be measured, and the hemoglobin level gradually decreased to 85 g/L. Considering the presence of erythrocyte agglutination, the cold agglutinin titer was measured as 1:128, a diagnosis of cold agglutinin disease was made.

After 4 days of treatment, the patient was weaned off the ECMO. Subcutaneous low molecular weight heparin was administered because of the relatively high levels of D-dimer (ranging from 2000 to 4000 μg/L). After the patient's vital signs were stable, he underwent pulmonary angiography and pulmonary emboli were found in the branches of the pulmonary artery on chest contrast-enhanced CT (Figure 1A 1C). We decided to continue administering subcutaneous low-molecular-weight heparin as anticoagulant therapy. No thrombosis of the abdomen or site of catheter placement was detected on ultrasound. Contrast-enhanced CT of the chest showed that the pulmonary emboli had decreased before discharge. The patient was discharged with the requirement for low-molecular-weight heparin. The coagulation function returned to normal, and chest CT findings were almost normal at the 1-month follow-up (Figure 1B 1D).

Discussion

The clinical manifestations of pulmonary embolism in children, especially young children, are generally nonspecific and often mimic the clinical symptoms of the underlying disease. The most frequent symptoms are dyspnea, chest pain, and cough.[2]; therefore, many thrombotic events may be missed without cardiorespiratory deterioration. However, the mechanism of thrombosis after M. pneumoniae infection remains unclear. Three mechanisms are currently considered to explain: (1) M. pneumoniae is present at the site of inflammation and local inflammatory cytokines induced by the pathogen; (2) M. pneumoniae is not present at the site of inflammation and immune modulations, such as autoimmunity or formation of immune complexes, play an important role; and (3) M. pneumoniae cases systemic hypercoagulable state and/or decreasing coagulation inhibitors.[1]

Cold agglutinin disease (CAD) is driven by cold agglutinins which are IgM autoantibodies binding to the I antigen on the surface of red blood cells (RBCs) at or just below the core body temperature.[3] The I antigen is contained in long-chain sialo-oligosaccharides, which serve as receptors for M. pneumoniae. These IgM antibody/antigen complexes interact with the C1 complex to activate the classical complement pathway, leading to the deposition of C3b, iC3b, and C3d opsonins on the RBC membrane. Thrombosis has largely been attributed to disruption and loss of the erythrocyte membrane, resulting in surface exposure of negatively charged phosphatidylserine (PS), which provides a surface for the formation of tenase and prothrombinase complexes. Increased surface PS also increased endothelial adherence and, therefore, could disrupt endothelial anticoagulant properties. Other factors, such as cytokine-induced expression of monocyte

or endothelial tissue factors, increase the incidence of venous thromboembolism.[4] Agglutination of RBCs also increases blood viscosity , causing reduced blood flow and stasis, which may contribute to the gradual formation of venous thrombosis.[3]

However, cold agglutinin syndrome in this child appeared during ECMO treatment, and pulmonary embolism was confirmed after the withdrawal of ECMO treatment, which made it difficult for us to connect cold agglutinin syndrome with pulmonary embolism. Central venous catheters are the most important risk factor for thromboembolism in children.[5] The following are the reasons why we consider the occurrence of pulmonary embolism associated with cold agglutinin syndrome: 1) Chest CT showed bilateral infiltrates, partial consolidation, and pleural effusion before ECMO treatment, which is the chest imaging change in the early stage of pulmonary thrombosis, and the area of lung involvement is not sufficient to cause severe hypoxemia, which could be explained by pulmonary embolism. 2) In ECMO treatment, the patient continued to receive heparin anticoagulant therapy and maintained blood hypocoagulability, which is contrary to our belief that cold agglutinin syndrome causes pulmonary embolism. 3) After anticoagulant treatment during ECMO, hypoxemia quickly resolved. ECMO treatment lasted only 4 days, which was far from the treatment process of acute respiratory distress syndrome caused by lung parenchymal injury due to M. pneumoniae. The hypoxemia was more in line with the manifestation of pulmonary embolism than with lung parenchymal injury caused by severe pneumonia.

In summary, a diagnosis of pulmonary embolism could easily be missed in a patient with M. pneumoniae pneumonia, whose symptoms of chest pain, shortness of breath, and pleural effusion could easily be attributed to pneumonia. Cold agglutinin disease triggered by mycoplasma infection may be the cause of pulmonary embolism. Patients with symptoms of pulmonary embolism and positive cold agglutinin after M. pneumoniae infection should be monitored for the possibility of thrombosis. Contrast-enhanced lung CT, echocardiography, and blood vessel ultrasonography should be routinely performed in such patients. It is important to diagnose patients earlier in their disease course as the long-term prognosis of thrombosis is good after the timely administration of anticoagulant therapy.

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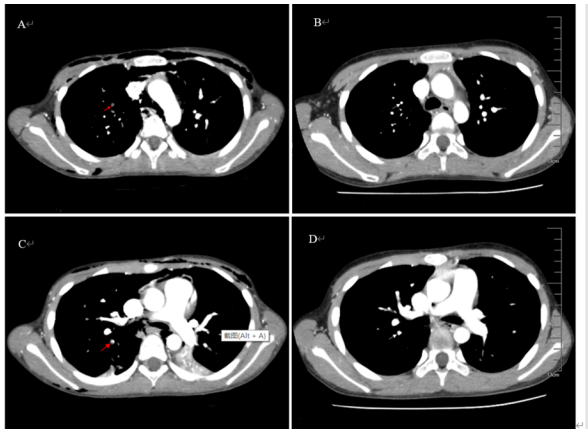

Figure1: Image changes of chest contrast-enhanced CT on the 4th day of admission and 1-month follow-up after discharge. A B Red arrow pointed pulmonary emboli. C D Pulmonary emboli disappeared at the same positon.