Pulmonary embolism triggered by cold agglutinin syndrome in mycoplasma pneumoniae pneumonia requiring VV ECMO treatment

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April 7, 2022

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. Finally, the patient was cured with antibiotic and anticoagulant therapies. Patients who have significantly increased C-reactive protein and D-dimer levels and positive cold agglutinin after M. pneumoniae infection should be monitored for the possibility of thrombosis formation.

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Funding:

National Natural Science Foundation of China, Grant/Award Number: 81771621;

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

Running head: Pulmonary embolism in M. pneumoniae pneumonia

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. Finally, the patient was cured with antibiotic and anticoagulant therapies. Patients who have significantly increased C-reactive protein and D-dimer levels and 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. Extrapulmonary manifestations involving every organ system (nervous, cardiovascular, arthritic, dermatological, digestive, hematological/hematopoietic, musculoskeletal, sensory, and urogenital) can occur.[1, 2] 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.[2] Most cases are treated conservatively, and there are few reports of the use of extracorporeal membrane oxygenation (ECMO). Herein, 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. Prior to admission, he received azithromycin for 5 days and cefmetazole sodium for 3 days. Chest examination revealed wheezing and prolonged expiratory time. After treatment in the outpatient clinic for 6 days, he developed dyspnea, his C-reactive protein level was raised to 68.36 mg/L, and bacterial infections could not be excluded. After all the treatments, the symptoms were not relieved. The patient was hospitalized because of cyanosis aggravation. On admission, the patient's vital signs were as follows: temperature, 37.9 °C; heart rate, 126 bpm; blood pressure, 98/58 mmHg; pulse oximetry, 90%; non-invasive ventilation setting, FiO2 50%; and 30 L/min oxygen flow. On general examination, the patient was found to be using his accessory muscles. 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. Initial laboratory tests showed a white blood cell (WBC) count of 9.6×109/L with neutrophilic predominance (82.9%), platelets 222×109/L, hemoglobin 12.5 g/dl, C-reactive protein 74.40 mg/L, procalcitonin 0.249 ng/mL, interleukin-6 34.16 pg/mL, lactate dehydrogenase (LDH) 690U/L, alanine transaminase (ALT) 145 U/L, aspartate transaminase (AST) 40.7 mg/L, partial thromboplastin (PT) time 13.1 s, activated partial thromboplastin time (aPTT) 24 s, international normalized ratio (INR) 1.2, fibrinogen 3.3 g/L, D-dimer 6611 ug/L, and fibrin degradation products (FDP) 40.7 mg/L. M. pneumoniae–specific immunoglobulin (Ig) M (5260 U/L) and IgG levels (119.469 U/mL) were elevated, and 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 bedside bronchoscopy treatment, and formation of bronchial casts could be seen on both sides of the tracheobronchial tree. In addition, stenosis was present at the entrance of the pulmonary segments, and the surface of the bronchi was partially congested and necrotic. When the obstruction was relieved by bronchoscopy,

the patient's oxygenation capacity continued to deteriorate and he was intubated for mechanical respiratory support. However, his respiratory status contributed to worsen, with lower vesicular breath sounds, and blood gas analysis showed hypoxemia and respiratory acidosis (pH 7.16, PCO2 89 mmHg, PO2 53 mmHg, HCO3- 31.7 mmol/L). The bedside chest radiograph showed that the pulmonary lesions did not aggravate significantly; therefore, bronchoscopy was performed for the second time to prevent the reformation of plastic. His oxygen saturation could not be maintained with mechanical ventilation (peak inspiratory pressure (PIP)/positive end expiratory pressure (PEEP) 28/8 mmHg, FiO2 1.0, respiratory rate: 25 bpm); therefore, he received VV ECMO. Tests of bronchoalveolar lavage fluid showed positive M. pneumoniae DNA. The WBC count raised to 29.3*109/L, and the D-dimer level increased to 19809 μg/L. 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, a diagnosis of cold agglutinin disease was made, and the titer was 1:128. We believe that refractory hypoxemia was related to this pathological change, and hypoxemia might have been caused by pulmonary embolism.

After 4 days of treatment, the patient was weaned off the ECMO. Oxygen saturation was maintained via nasal cannula. Subcutaneous low molecular weight heparin was administered because of the relatively high levels of D-dimer (ranging from 2000 to 4000 μg/L). His fever had gone and the levels of C-reactive protein, procalcitonin, interleukin-6, and lactate dehydrogenase improved. He was taken off of antibiotics and methylprednisolone on the day of extubation. 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. By the eleventh day, he was weaned off nasal cannula oxygen inhalation. On the fifteenth day of admission, C-reactive protein, procalcitonin, lactate dehydrogenase, ALT, and AST were back to normal. Additionally, coagulation function returned to normal levels. 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

M. pneumoniae is responsible for up to 40% of community-acquired pneumonia cases in children over 5 years of age.[1] Extrapulmonary manifestations involving every organ system can occur, including cardiac and aortic thrombi as cardiovascular manifestations; erythema nodosum, cutaneous leukocytoclastic vasculitis, and subcorneal pustular dermatosis as dermatological manifestations; acute cerebellar ataxia, opsoclonus-myoclonus syndrome, and thalamic necrosis as neurological manifestations; pulmonary embolism as a respiratory system manifestation; and renal artery embolism as a urogenital tract manifestation. Three mechanisms are currently considered to explain these extrapulmonary manifestations: (1) a direct type, in which the bacterium is present at the site of inflammation and local inflammatory cytokines induced by the bacterium play an important role; (2) an indirect type, in which the bacterium 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) a vascular occlusion type, in which vasculitis and/or thrombosis with or without systemic hypercoagulable state induced by the bacterium plays an important role.[2, 3] Cold-agglutinin hemolytic anemia is the result of IgM antibodies directed against the I antigens on the erythrocyte surface.[2] Patients with cold agglutinin disease are at an increased risk of thrombotic events.[4] To our knowledge, there have been no cases of pulmonary embolism associated with cold agglutinin disease in M. pneumoniae infection.

The clinical manifestations of pulmonary embolism vary and lack specificity. Patients with mild pulmonary embolism may be asymptomatic, while severe cases may suffer from pulmonary arterial hypertension, unstable hemodynamics, or even sudden death.[5, 6] The most frequent symptoms are dyspnea, chest pain, and cough.[7, 8] The clinical manifestations of pulmonary embolism in children, especially young children, are

generally nonspecific and often mimic the clinical symptoms of the underlying disease; therefore, many thrombotic events may be missed without cardiorespiratory deterioration. However, the mechanism of thrombosis after M. pneumoniae infection remains unclear. Autoimmune vasculitis or immune-mediated inflammation of the arterial wall may play an underlying mechanism.[9] M. pneumoniae is transferred to the pulmonary artery, inducing cytokines (such as tumor necrosis factor-a) and chemokines (such as interleukin-8) at the local site through the function of lipoproteins contained in the bacterial cell membrane, which eventually causes local vasculitic and/or thrombotic vascular occlusion without a systemic hypercoagulable state.[2] Mycoplasma also causes a hypercoagulable state indirectly. It is suggested that the antibodies created in response to Mycoplasma infection form immune complexes that cause an inflammatory response in the pulmonary arteries, leading to endothelial damage and the subsequent release of procoagulants.[8] In vitro experimental studies have suggested that lipoglycans from some mycoplasmas can induce procoagulant activity through the expression of tissue factors in human mononuclear cells, leading to increased procoagulant activity in these patients.[10] M. pneumoniae infection can lead to transient elevation of antiphospholipid antibodies, which is commonly seen in systemic lupus erythematosus and is associated with an increased risk of both arterial and venous thrombosis.[11] Additionally, some physiological coagulation inhibitors, including protein C system and tissue factor pathway inhibitors, may be impaired.[2]

Autoimmune hemolytic anemia (AIHA) is a disorder characterized by autoantibody-mediated hemolysis. Cold agglutinin disease (CAD) is a form of complement-mediated AIHA, in which the pathophysiology is driven by IgM autoantibodies binding to the I antigen on the surface of red blood cells (RBCs) at or just below the core body temperature.[1, 4, 12, 13] The I antigen is contained in long-chain sialo-oligosaccharides, which serve as receptors for M. pneumoniae. Cold agglutinins are IgM antibodies directed against I antigens.[14] 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. The majority of opsonin-coated RBCs are removed from circulation by the mononuclear phagocyte system, resulting in extravascular hemolysis. Classical pathway activation may proceed to the terminal portion of the complement pathway on some RBC membranes, resulting in the formation of a membrane attack complex (C5b-9) and intravascular hemolysis.[4] Hemolytic anemia associated with multiple vascular thromboses is a rare but severe complication of M. pneumoniae.[9] Thrombosis in autoimmune hemolytic anemia 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.[15] Agglutination of RBCs also increases blood viscosity , causing reduced blood flow and stasis, which may contribute to the gradual formation of venous thrombosis.[12] Therefore, when the cold agglutinin antibody titer is high, attention should be paid to the possibility of autoimmune hemolysis and thrombosis.

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.[16] Despite improvements in ECMO technology, bleeding and thrombosis remain significant complications as the interaction between the patient's native blood and the foreign surface of the ECMO circuit activates the coagulation cascade.[17] We use continuous unfractionated heparin infusion (5–20 U/kg/h) for the anticoagulation protocol. The target ACT range was 180–200 s to monitor anticoagulation.

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,[18] 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.

The American Society of Hematology guideline panel recommends using anticoagulants in pediatric patients with symptomatic deep vein thrombosis or pulmonary embolism when hemodynamics are stable. Thrombolysis followed by anticoagulation is recommended for pediatric patients with pulmonary embolism and hemodynamic compromise.[19] After ECMO treatment, pulmonary embolism was confirmed, the hemodynamics of the child were stable; thus, low-molecular-weight heparin was continued for anticoagulant therapy, and the pulmonary embolism gradually disappeared after the follow-up. If the diagnosis of pulmonary embolism was confirmed earlier and thrombolytic drugs actively used, our patient could have avoided uncorrectable hypoxemia and ECMO treatment.

There were some limitations in our case study. Inherited thrombophilia (IT) is strongly associated with venous thromboembolism. IT, including factor V Leiden mutation, prothrombin G20210A mutation, antithrombin deficiency, protein C deficiency, and protein S deficiency were not tested in our patient. However, the impact of these disorders on thromboembolism development in children remains poorly defined and controversial.

In summary, M. pneumoniae is a common community-acquired pathogen. A diagnosis of pulmonary embolism could easily be missed in a patient with pneumonia, whose symptoms of chest pain, shortness of breath, and pleural effusion could easily be attributed to pneumonia. In addition, some patients may be asymptomatic. 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. Cases of M. pneumoniae infection leading to subclinical thrombi are likely to be higher than reported, and more sensitive means of examination are yet to be explored. Moreover, whether magnetic resonance imaging provides new evidence for these pathological changes remains under study. 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.

Acknowledgements

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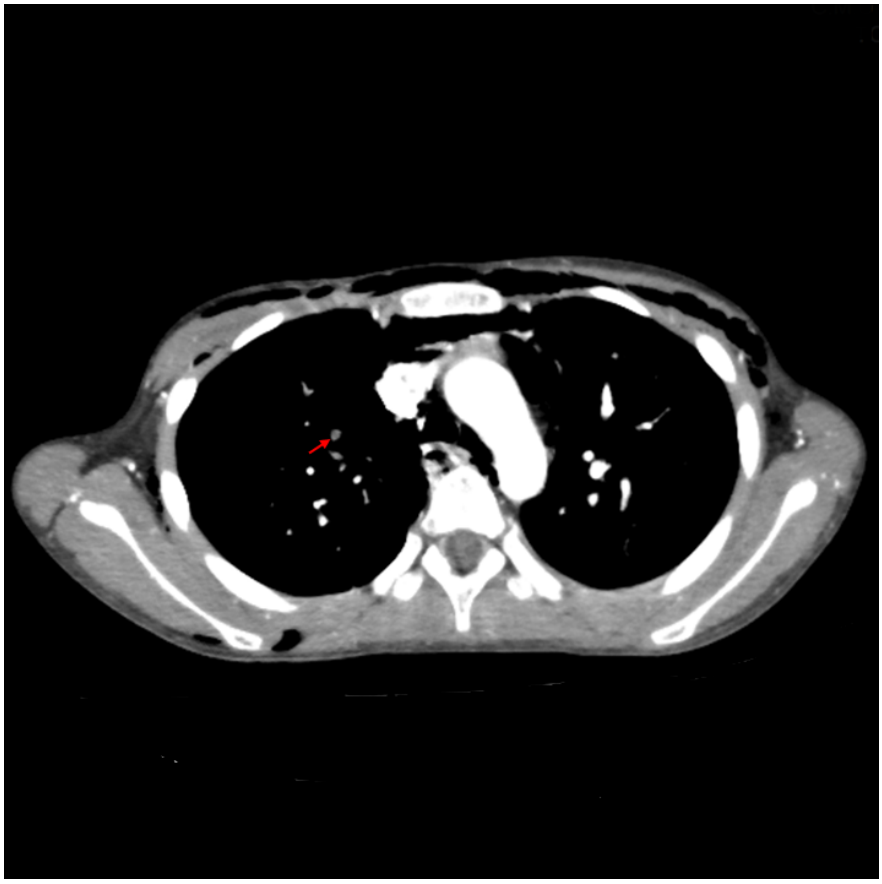
1A



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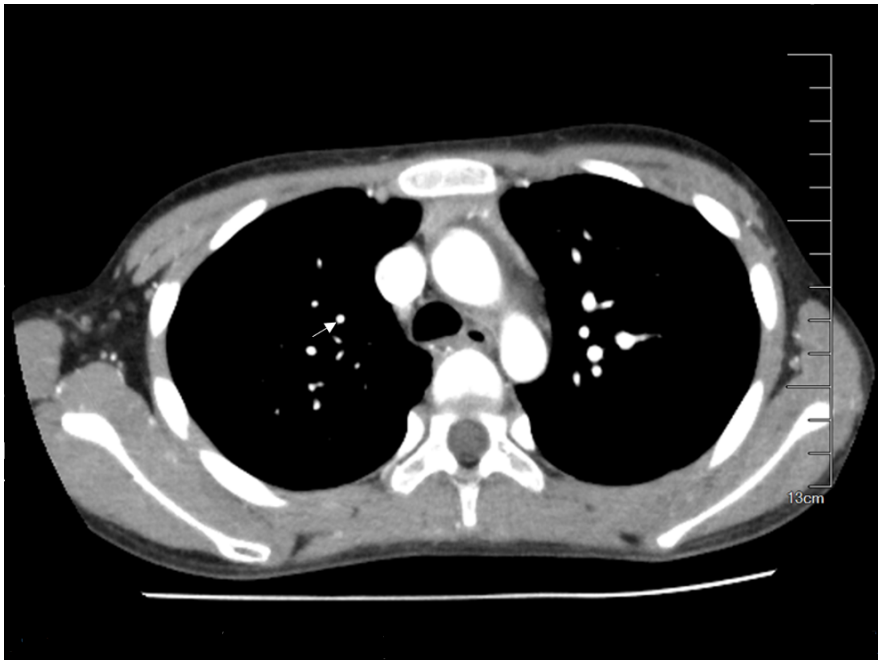

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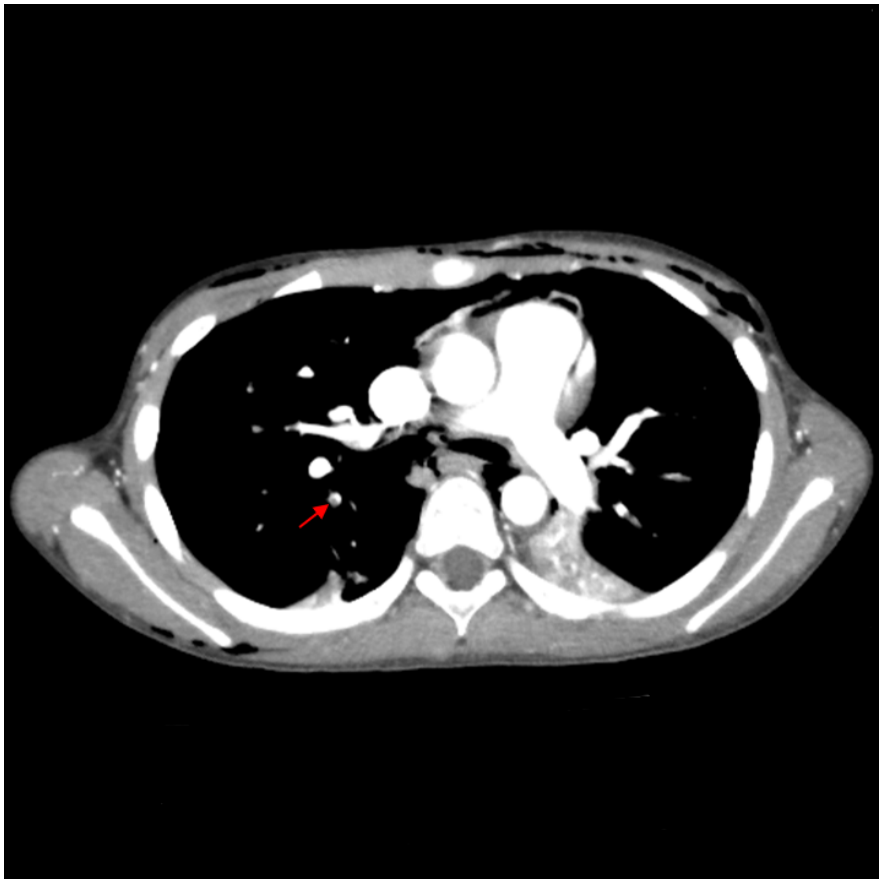

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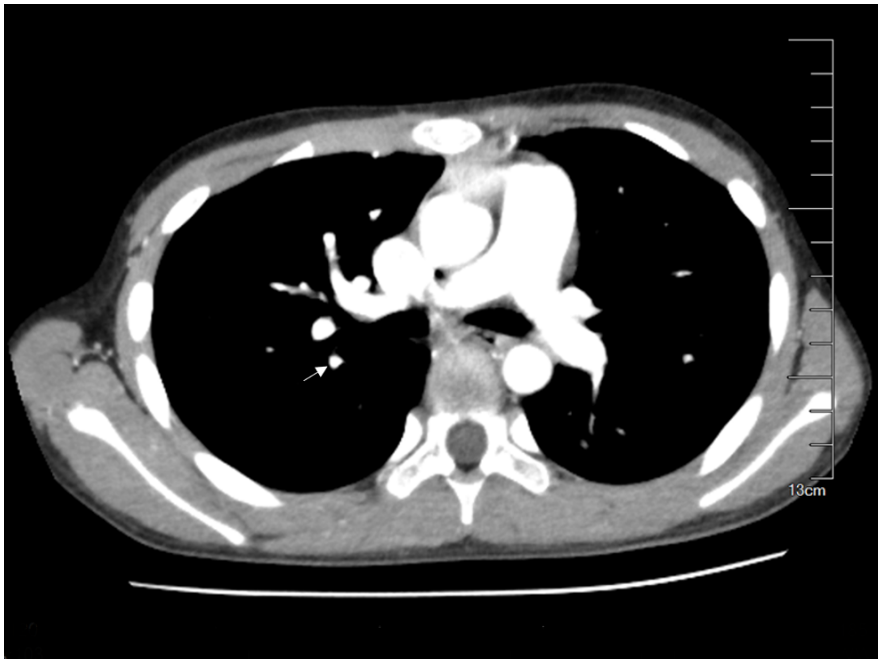

Figure1: Image changes of chest contrast-enhanced CT on the 4th day of admission and 1-month follow-up after discharge. A B Red arrow pointed pulmonary emboli. C D Pulmonary emboli disappeared at the same positon.

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