Characteristics and Outcomes of Mycoplasma Pneumoniae Pneumonia Associated with Pulmonary Embolism and Necrotizing Pneumonia in Children

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Purpose: To explore the clinical characteristics, treatment, and long-term prognosis of mycoplasma pneumoniae pneumonia (MPP) combined with pulmonary embolism (PE) in children.

Patients and Methods: The medical records of 16 children who were diagnosed with MPP associated with PE between January 2016 and January 2023 at Children’s Hospital, Zhejiang University School of Medicine were retrospectively reviewed.

Results: The average age patients were 8.24 ± 1.99 years. All cases were diagnosed with refractory mycoplasma pneumoniae pneumonia (RMPP) and presented complications in the form of necrotizing pneumonia (NP). The main symptoms observed were cough and fever (n = 16, 100%), chest pain (n = 8, 50%), dyspnea (n = 8, 50%), and hemoptysis (n = 4, 25%). In these cases, 12 patients had involvement of the pulmonary artery, 3 patients experienced issues with the pulmonary vein, and 1 patient had simultaneous involvement of both the pulmonary artery and pulmonary vein. Among the 12 pulmonary artery embolism cases, 6 involved the right pulmonary artery, 4 involved the left pulmonary artery, and 2 involved both the right and left pulmonary arteries. The mean D-dimer level was 8.50 ± 4.76 mg/L. All patients received anticoagulant therapy, and after treatment, there was a significant improvement in their symptoms and lung lesions.

Conclusion: Children with RMPP, chest pain, hemoptysis, and elevated D-dimer levels should be closely monitored for the potential development of PE. The co-occurrence of MPP and PE often involves the presence of NP. In cases of confirmed PE, anticoagulation therapy may be a suitable consideration. PE and NP resulting from MPP generally had a favorable overall prognosis.

Keywords: mycoplasma pneumoniae, pulmonary embolism, necrotizing pneumonia, children

Introduction
Mycoplasma pneumoniae (MP) is an important pathogen of respiratory tract infections that can cause up community-acquired pneumonia (CAP) in children.1,2 Typically, mycoplasma pneumoniae pneumonia (MPP) is characterized by mild, self-limiting symptoms. However, there have been recent cases where MPP has led to both pulmonary and extrapulmonary complications, such as necrotizing pneumonia (NP), pulmonary embolism (PE), cerebral infarction, myocarditis, hemolytic anemia, Stevens–Johnson syndrome, and erythema multiforme.3–5 PE is one of the rarest extrapulmonary complications that has been reported in previous studies. However, few literature had concentrated on MPP associated with PE. Here, we describe 16 pediatric MPP associated with PE cases with diverse clinical manifestations. The aim of this study is to advance clinical experience for the diagnosis and treatment of such diseases.
Materials and Methods

Study Population

In this study, we retrospectively collected the clinical data of 16 MPP patients with PE who were admitted to Children’s hospital, Zhejiang University School of Medicine between January 1, 2016, and January 31, 2023.

We collected relevant information including medical manifestations, inflammatory indicators such as C-reactive protein (CRP) and lactate dehydrogenase (LDH), and the results of blood coagulation studies such as D-dimer levels, Protein C activity, Protein S activity and Antithrombin-III. Besides, the results of contrast-enhanced lung CT, blood vessel ultrasonography, treatments and outcomes were all recorded.

CT was performed using 64-MDCT scanners (GE, America) for all patients, and the standard scanning parameters were as following: slice thickness of 0.625 mm, 1.375 pitch120 kV , and automated mA. Philips iE33 type (probe frequency 1 ~ 5 MHz, load Blue Royal Philips), Vivid E9 (probe frequency 3 ~8 MHz, US GE) Doppler ultrasonic diagnostic instrument for detection survey.

Diagnostic Criteria

The diagnostic standard for MPP was defined as follows:6,7 (1) signs and symptoms indicative of CAP, including fever, cough, abnormal lung auscultation and new infiltrate(s) on chest radiograph; (2) had both positive results for MP RNA or DNA polymerase chain reaction (PCR) tests and positive results for MP-IgM. Patients with congenital pulmonary disease, chronic cardiac and pulmonary disease, rheumatic diseases, immunodeficiency, a family history of thrombophilia and incomplete medical records were excluded.

The diagnosis standard of NP mainly depends on the chest computed tomographic (CT) characteristics,8–10 including the destruction of normal pulmonary parenchymal architecture and the presence of areas of decreased parenchymal enhancement, representing liquefaction, that are gradually replaced by multiple small air or fluid filled-cavities.

Refractory mycoplasma pneumoniae pneumonia (RMPP) was defined as having prolonged fever and deterioration of clinical and radiological findings after reasonable antimicrobial therapy for 7 days or more.11

Statistical Analyses

We performed statistical analyses by using SPSS software (version 25.0). Normal distribution data were expressed as mean ± SD, which were compared by independent-Samples $t$-test. Skewed distribution data were expressed as median values (25th-75th interquartile ranges), which were compared by the Mann–Whitney $U$-test.

Ethical Considerations

The study was approved by the Ethics Committee of Children’s Hospital and Zhejiang University School of Medicine, and Informed consent was obtained from guardian of all the patients at the beginning of admission to our department (2023-IRB-0039-P-01). This study adhered to the Declaration of Helsinki’s ethical standards.

Results

General Information and Clinical Characteristics of Patients

The average age patients were 8.24 ± 1.99 years with a male/female ratio of 1:1, as presented in Table 1. The duration of disease prior to hospitalization in our department was 6–30 days. PE occurred between the 12th and the 36th day after the disease onset. All patients were diagnosed with RMPP. The patients presented with persistent high fever and cough (n = 16, 100%), chest pain (n = 8, 50%), dyspnea (n = 8, 50%), haemoptysis (n = 4, 25%), abdominal pain (n = 5, 31%) and headaches (n = 2, 12.5%) (Table 1). Twelve of the 16 patients had extrapulmonary complications, including liver function abnormalities in 10 cases, pericardial effusion in 4 cases, rash in 4 cases, encephalitis in 1 case, splenic infarction in 1 case and axillary vein thrombosis in 1 case.
Laboratory Findings of Patients

The initial serum biochemistry findings for these cases are presented in Table 1. The average white blood cell count (WBC) was 12.04 ± 5.56×10^9/L, with a mean neutrophil (N) percentage of 76.34 ± 11.54%. Mean CRP levels were recorded at 24.64 ± 57.63mg/L. In all 16 cases, LDH levels were elevated at 595.50 ± 232.35 IU/L. Elevated alanine aminotransferase (ALT) levels were found in 68.75% (11/16) of patients. D-dimer levels had an average of 8.50 ± 4.76mg/L, with 31.25% (5/16) of patients having D-dimer levels exceeding 10.00 mg/L, and 87.50% (14/16) of patients had levels exceeding 5.0 mg/L (Table 1). Furthermore, among the patients, antinuclear antibodies (ANAs) tested positive in 50% (2/4) of cases, with both displaying a titer of 1:320. Additionally, 4 children underwent screening for anticardiolipin antibodies (ACA), and 1 child had an elevated level of anticardiolipin IgM (ACL-IgM). Furthermore, one of these individuals exhibited elevated levels of ACL-IgA and beta-2-glycoprotein antibodies. Moreover, protein S activity, Protein C activity, and Antithrombin-III were assessed in 8 children, revealing that 62.5% (5/8) of them had low protein S activity, while Protein C activity and Antithrombin-III levels were within the normal range.

Radiographic Features of Patients

Pulmonary inflammatory consolidation and pleural effusion were observed in 100% (16/16) of patients. NP manifested in all 16 patients within a period of 15 to 40 days following the disease onset. Atelectasis was observed in 10 cases, and pneumothorax occurred in 3 cases. PE occurred on the same side as the pulmonary consolidation in 56.3% (9/16) of patients (Table 1). The Pulmonary Artery (PA) was the most commonly involved vessel. In 12 patients, only the PA was affected, with 6 cases on the right, 4 cases on the left, and 2 cases on both sides (Figure 1). Among the 12 patients, PA thrombosis coincided with the side of pulmonary consolidation in 5 of these cases (Figure 2). In 3 patients, only the Pulmonary Vein (PV) was involved, with 2 cases on the right and 1 on the left. Notably, 1 case displayed a filling defect at the entrance of the left atrium and the left pulmonary vein (Figure 1). One case had a filling defect in the left lower pulmonary artery complicated with a spleen infarction (Figure 3). In all instances of PV thrombosis, it occurred on the same side as the pulmonary consolidation. Furthermore, 1 patient experienced simultaneous PA and PV thrombosis.
After admission, all patients received macrolides for treatment. In order to harness their anti-inflammatory properties, methylprednisolone (1–4mg/kg/d) was administered to all individuals. Anticoagulant therapy with low molecular weight heparin (LMWH) was initiated for all cases. Warfarin was prescribed for 10 patients, and the dosage was adjusted based on INR results. Additionally, bronchoscopy was performed on 13 patients, revealing the presence of viscous secretions in all patients, mucus plugs in 6 patients, plastic bronchitis in 3 patients, and necrotizing bronchitis in 2 patients.

In the 8 months to 5 years of follow-up, there were no reported deaths or cases of recurrent thrombosis among the children. Thrombus absorption took more than 1 month in 11 patients and less than 1 month in 5 patients. However, thrombosis-related symptoms, including hemoptysis and chest pain, resolved within two weeks in 15 patients.

**Discussion**

In this study, we conducted a retrospective analysis of 16 cases of severe MPP complicated by PE. Previous research has identified two distinct peaks in the incidence of PE among children, namely during the neonatal period and adolescence. Notably, the median age of the children involved in our study was 8 years old, a statistic that is likely correlated with the increased prevalence of MPP among school-age children.

PE in children can present with various symptoms, including cough, shortness of breath, hemoptysis, and chest pain, among others. Physical signs may include an elevated heart rate, increased respiration, and hypoxia. However, these manifestations may also be absent. In our study, we observed that among the 16 children diagnosed with PE, 16 exhibited cough, 4 experienced hemoptysis, 4 reported shortness of breath, and 8 complained of chest pain. Additionally, some patients

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**Figure 1** Chest CTA showed a filling defect (red arrow) in the right pulmonary artery and left pulmonary artery (A). Chest CTA showed a filling defect (red arrow) in the right pulmonary artery (B and C). Chest CTA showed a filling defect (red arrow) in the entrance of left atrium and left pulmonary vein (D and E).

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displayed no specific symptoms, a finding consistent with existing literature. Early detection of PE in children poses a challenge. Multiple studies have shown that diagnosing this condition in children is often delayed or missed, with diagnoses typically occurring seven days later than in adults.\textsuperscript{13,17} In our study, 12 out of the 16 children displayed symptoms such as cough, shortness of breath, and hemoptysis after their body temperature had returned to normal, or they developed new symptoms like hemoptysis and chest pain. Remarkably, the time to diagnosis ranged from 12 to 36 days into the course of the disease. Consequently, when managing clinically severe MPP over a span of 2 to 5 weeks, healthcare providers should remain vigilant for the aforementioned symptoms, as they may indicate the presence of PE.

Currently, the mechanism underlying vascular embolization in MPP remains obscure. MP may induce microvascular endothelial injury and provoke the release of cytokines, resulting in localized vasculitis and thrombotic vascular occlusion. The cell membranes of MP contain immunogenic components like glycolipids and glycoproteins that share antigens with human tissues, stimulating the production of autoantibodies, and the immune complex is formed potentially causing damage to various organs beyond the lungs, including the respiratory tract. Alternatively, MP may activate the complement system, which in turn triggers the coagulation cascade, ultimately resulting in thrombus formation. Research has indicated that autoimmune reactions triggered by MP infection are responsible for the generation of significant players in thrombosis, including antiphospholipid antibodies (aPL) and ANAs.\textsuperscript{18,19} Notable examples of antiphospholipid antibodies encompass ACA, lupus anticoagulant (LA), and β2-glycoprotein antibodies. Previous study\textsuperscript{5} have confirmed this mechanism, and this study concluded that mycoplasma pneumoniae infection can cause vascular endothelial cell damage and autoimmune reactions, resulting in temporary hypercoagulability and thrombosis. Furthermore, MP infection

\textbf{Figure 2} Chest X-ray showed right side pneumonia (A) Chest CT showed consolidation of the lower lobe of the right lung (B) Chest CTA showed a filling defect (red arrow) in the right lower pulmonary artery (C).
can lead to hepatocyte damage, hypoxia, and immune-related injuries, potentially augmenting the synthesis of endogenous coagulation factors. Concurrently, there may be a reduction in the synthesis of critical anticoagulation factors like antithrombin III (AT-III), protein C, and protein S.\textsuperscript{15} Cases involving elevated coagulation factors and anomalous anticoagulation proteins have also been documented in the context of MP infection coupled with embolism.\textsuperscript{5,16} Notably, half of the pulmonary thrombosis patients developed on the same side as the pulmonary consolidation in our study, further supporting the hypothesis that isolated arterial thrombosis may be in situ thrombosis.\textsuperscript{5,20} To date, rare studies investigating in situ thrombosis and consolidation in MPP have been reported, and such studies may guide future mechanism research.

D-dimer is the smallest fragment of fibrin degradation products. Increased levels indicate a hypercoagulable state and active fibrinolysis, which is crucial for the early diagnosis of thrombotic diseases. A study involving children aged 5 to 17 years reported that D-dimer had a sensitivity of 100% and a specificity of 58% in diagnosing acute PE in children, making it particularly valuable for ruling out the condition in those without high-risk factors.\textsuperscript{21} In our study, the concentration of D-dimer was measured at $8.50 \pm 4.76$ mg/L. D-dimer levels exceeded 10.0 mg/L in 31.25% (5 out of 16) of patients and surpassed 5.0 mg/L in 87.5% (14 out of 16) of patients, aligning with findings in the existing literature.\textsuperscript{5,22}

Angiography is the gold standard for diagnosing deep venous thrombosis and pulmonary embolism; however, due to its invasion and potential risks, its clinical applicability in children is limited.\textsuperscript{23,24} In our study, all 16 children were diagnosed with PE through the use of computed tomography pulmonary angiography (CTPA), a highly sensitive and specific technique that is currently the most prevalent method for confirming PE diagnoses. PE typically presents as a filling defect within the

Figure 3 Chest X-ray showed right side pneumonia (A) Chest CTA showed a filling defect (red arrow) in the left lower pulmonary artery (B) Abdominal enhanced CT shows partial non-enhancement of the spleen, suggestive of splenic infarction (C).
affected blood vessels, and in some instances, this defect may appear sparse. In our study, CTPA examinations of 16 children revealed the presence of vascular filling defects. Specifically, in 9 cases, PE was localized within the region of lung consolidation, whereas in 7 cases, the embolic site did not coincide with the side of lung consolidation.

The treatment of PE in children often draws from the findings and approaches established in adult studies. In cases where children present with MPP complicated by PE, the current standard practice includes the administration of anticoagulation therapy alongside treatment for the underlying primary disease. Anticoagulation stands as the primary therapeutic approach for children with hemodynamically stable PE. Commonly employed anticoagulants include LMWH, unfractionated heparin (UFH), vitamin K antagonists (eg, warfarin), factor Xa inhibitors and direct thrombin inhibitors. After the initiation of parenteral anticoagulation (eg, UFH or LMWH), the addition of oral anticoagulants such as warfarin is typically recommended. For patients undergoing warfarin therapy, it is crucial to monitor the international normalized ratio (INR) and maintain it within the range of 2–3. It is worth noting that vitamin K antagonists like warfarin, while effective, have limited use in children due to challenges associated with dietary restrictions, laboratory monitoring, and concerns about teratogenicity. In recent developments, direct oral anticoagulants (DOACs) have emerged as promising alternatives for antithrombotic therapy. DOACs, including dabigatran, argatroban, bivalirudin, rivaroxaban, apixaban, and edoxaban, offer enhanced anticoagulant efficacy and reduced bleeding risk. In our study, both LMWH and warfarin were employed to treat 15 children with PE. During the follow-up period, no adverse effects such as bleeding, liver or kidney damage were observed, and late follow-up revealed gradual thrombus absorption. Nonetheless, one patient experienced new hemoptysis after being on warfarin for 2 weeks, and CTPA review revealed the presence of thrombolysis. Consequently, the decision was made to discontinue warfarin treatment. Subsequent follow-up assessments showed that PE did not recur, and the patient’s symptoms gradually improved. Therefore, whether anticoagulant therapy is necessary for infective PE remains to be explored.

NP has been previously documented as a complication of MPP, characterized by the underlying destruction and necrosis of lung tissue. Our study findings indicate that all 16 cases of PE were accompanied by necrotic pneumonia, suggesting a potential link between NP and the pathogenesis of PE. The pathogenesis of NP involves the occlusion of pulmonary artery branches and alveolar capillaries by inflammation, which subsequently leads to ischemia and necrosis within the pulmonary parenchyma. Following this necrotic process, cavities may form as necrotic material is discharged. It is important to note that as of now, there is no existing literature that specifically addresses this association.

Children with RMPP, chest pain, hemoptysis, and elevated D-dimer levels should be closely monitored for the potential development of PE. When there is suspicion of PE, conducting a CTPA examination can be valuable for diagnosis. When MPP is combined with PE, NP is often present. In cases of confirmed PE, anticoagulation therapy with successive LMWH treatment may be a suitable consideration.

This study has several limitations. First, it is a retrospective study, and the examination data of some children are incomplete. Second, the sample size is small; the patients enrolled are from a single center, and we need to further follow-up large sample prospective studies.

Conclusion
In conclusion, PE caused by mycoplasma pneumoniae infection with atypical early symptoms. We should dynamically test coagulation indexes and perform chest ultrasound and CTA to confirm the diagnosis and provide effective anticoagulant therapy early to reduce complications and improve prognosis. PE caused by mycoplasma pneumoniae have a good overall prognosis, although the clinical symptoms are relatively severe.

Abbreviations
MP, mycoplasma pneumoniae; CAP, community-acquired pneumonia; MPP, mycoplasma pneumoniae pneumonia; NP, necrotizing pneumonia; PE, pulmonary embolism; CAP, C-reactive protein; LDH, lactate dehydrogenase; PCR, polymerase-chain reaction; CT, computed tomographic; RMPP, refractory mycoplasma pneumoniae pneumonia; WBC, white blood cell count; N, neutrophil; ALT, alanine aminotransferase; ANAs, antinuclear antibodies; ACA, anticardiolipin antibodies; ACL-IgM, anticardiolipin IgM; PA, pulmonary artery; PV, pulmonary vein; LMWH, low molecular weight heparin; aPL, antiphospholipid antibodies; LA, lupus anticoagulant; AT-III, antithrombin III; CTPA, computed tomographic pulmonary angiography.
tomography pulmonary angiography; UFH, unfractionated heparin; INR, international normalized ratio; DOACs, direct oral anticoagulants.

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**Disclosure**

The authors report no conflicts of interest in this work.

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