Infection and Drug Resistance Dovepress

Open Access Full Text Article

CASE REPORT

Massive Deep Venous Thrombosis in a Child with Necrotizing Pneumonia Due to Mycoplasma Pneumonia Infection

Shuang Li[1,*], Guolan Huang[1,*], Yongping Xie[1], Xinghui Yang[2], Can Lai[2], Lisu Huang[1]

[1]Department of Infectious Disease, Children's Hospital of Zhejiang University School of Medicine, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Radiology, Children's Hospital of Zhejiang University School of Medicine, National Clinical Research Center for Child Health, National Children's Regional Medical Center, Hangzhou, Zhejiang, People's Republic of China

*These authors contributed equally to this work

Correspondence: Lisu Huang, Department of Infectious Disease, Children's Hospital of Zhejiang University School of Medicine, No. 3333 Binsheng Road, Binjiang District, Hangzhou, Zhejiang, 310052, People's Republic of China, Email lisuhuang@zju.edu.cn; Can Lai, Department of Radiology, Children's Hospital of Zhejiang University School of Medicine, No. 3333 Binsheng Road, Binjiang District, Hangzhou, Zhejiang, 310052, People's Republic of China, Email childrenrad@zju.edu.cn

Abstract: Thrombosis is uncommon but increasingly recognized complication in pediatric patients with *Mycoplasma pneumoniae* (*M. pneumoniae*) infection. In general, small-vessel thrombosis is treated by medication therapy. However, the management of thrombosis in large vessels is more complex and controversial due to the risks of thrombus enlargement and embolization. In this case, we report an 8-year-old boy who was hospitalized for macrolide-resistant *M. pneumoniae* pneumonia. After experiencing abdominal pain, he was diagnosed with thrombosis in the pulmonary artery and mesenteric vein. Additionally, massive thrombi were found in the inferior vena cava and left common iliac vein, measuring approximately 4 cm and 4.5 cm in length, respectively. Following routine therapies of anti-infection and anticoagulation, the patient continued to experience recurrent abdominal pain, and there was a risk of the deep vein thrombi detachment. To avoid the shedding of thrombi, the patient underwent inferior vena cava filter placement and catheter-directed thrombolysis with alteplase on day 8 following admission. The clinical symptoms significantly improved, and thrombosis recurrence was not observed in the subsequent follow-ups. This case report highlights the need for prompt recognition of thrombosis in *M. pneumoniae* infection. Massive thrombus in deep vein is extremely rare but life-threatening in children. The optimal treatments remain to be determined due to the limited experience to date.

Keywords: children, Mycoplasma pneumoniae, deep venous thrombosis, thrombolysis

Background

Mycoplasma pneumoniae (*M. pneumoniae*) is one of the world's leading causes of community-acquired pneumonia in children and adolescents.[1,2] In recent years, the emergence of macrolide-resistant *M. pneumoniae* has brought renewed focus and concern. Patients with *M. pneumoniae* pneumonia will have pulmonary manifestations; however, nearly 50% of the hospitalized patients develop various extrapulmonary complications, mainly gastrointestinal, dermatological, and neurological.[3] Venous and arterial thrombosis is an uncommon but increasingly recognized life-threatening complication. Thrombosis occurs mostly in pulmonary vasculature and rarely occurs in large veins of the lower extremities or pelvis.[4] The management of serious complications arising from *M. pneumoniae* infection is complicated and controversial. Here, we describe a rare case of macrolide-resistant *M. pneumoniae* infection complicated with necrotizing pneumonia, pulmonary embolism, and massive thrombi in deep veins.

Received: 28 June 2024
Accepted: 12 November 2024
Published: 28 November 2024

Case Presentation

An 8-year-old boy, previously in good health, presented with a 13-day history of high-grade fever and wet coughing. Despite receiving intravenous azithromycin (10 mg/kg/day) for 7 days and a short course of systemic corticosteroids prior to admission, his symptoms did not improve. On the day before admission, he developed lower abdominal pain and profuse sweating. Coagulation analyses revealed a D-dimer level of 6.66 mg/L, prompting his admission to the Department of Infectious Diseases at Children's Hospital, Zhejiang University School of Medicine for further evaluation and management. Physical examination upon admission revealed pulmonary crackles and tenderness in the lower abdomen. He underwent laboratory tests and imaging examinations. The oropharyngeal swab PCR result confirmed the presence of macrolide-resistant *M. pneumoniae*, with a mutation in the 23S rRNA gene identified. Enhanced computed tomography (CT) scans revealed necrotizing pneumonia in both lungs and multiple thrombi in the pulmonary arteries (Figure 1A), mesenteric vein (Figure 1B), inferior vena cava (Figure 1C), and left common iliac vein (Figure 1D). The thrombi located in the inferior vena cava and the left common iliac vein were approximately 4 cm and 4.5 cm in length, respectively. The thrombus nearly completely blocked the left common iliac vein (Figure 1E).

The patient received treatment that included levofloxacin and a short course of dexamethasone. After treatment, the presenting symptoms, including fever and cough, rapidly improved. To prevent excessive thrombus formation, nadroparin calcium was initiated upon admission, and oral rivaroxaban was added to the subsequent treatment regimen. After 5 days of therapy, the D-dimer level decreased to 3.41 mg/L. However, the patient reported recurrent abdominal pain. Vascular ultrasound revealed an exacerbation of deep vein thrombosis with a risk of shedding (Figure 2). We organized multidisciplinary discussions, and the patient was referred for surgery, undergoing inferior vena cava filter placement on day 8 following admission. Simultaneously, catheter-directed thrombolysis with a total alteplase dose of 20 mg (for a body weight of 34 kg) was administered in conjunction with a continuous heparin infusion (Supplementary Video 1). The alteplase infusion via the left femoral vein catheter was administered over 2 hours, allowing direct delivery to the thrombus site. Intraoperative angiography performed every half hour showed that the thrombi in the inferior vena cava and left common iliac vein dissolved effectively. The patient was transferred to the intensive care unit and continued to

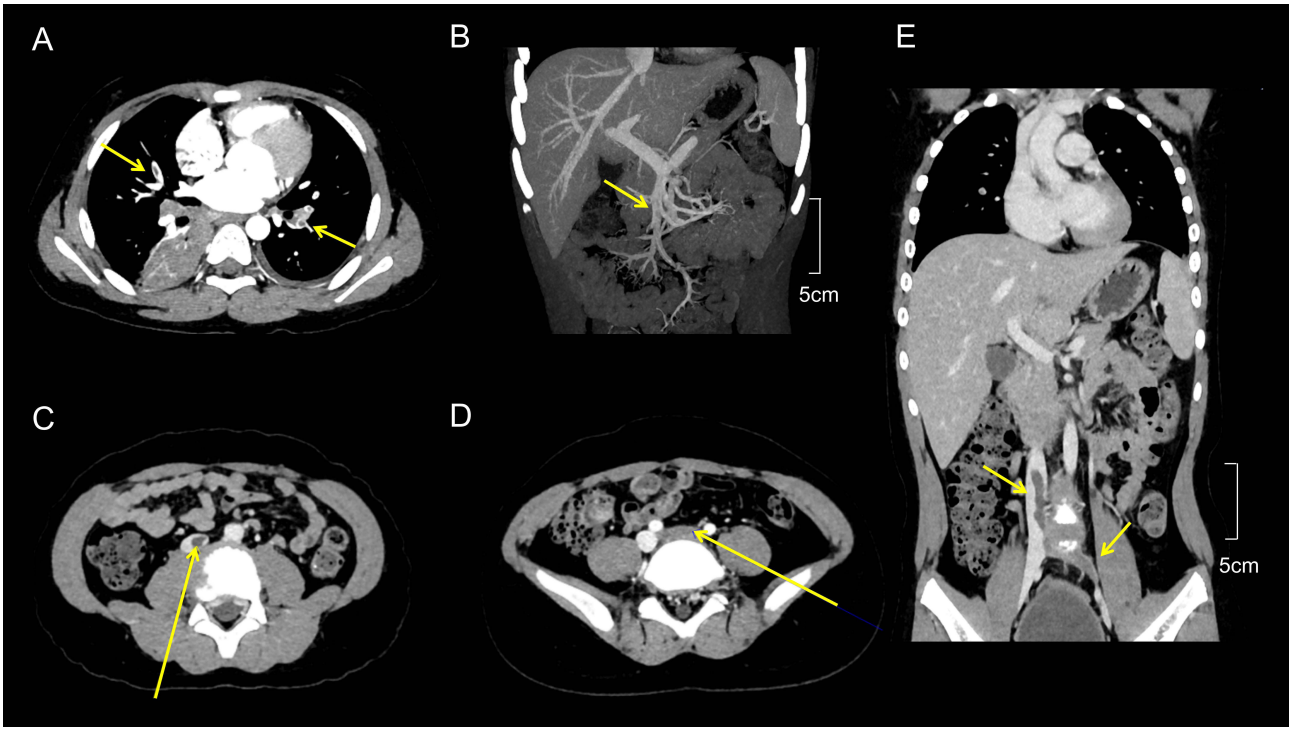

Figure 1 The computed tomography angiography reveals the thrombi in the left and right pulmonary arteries (**A**), mesenteric vein (**B**), inferior vena cava (**C**), and left common iliac vein (**D**). The thrombi in the inferior vena cava and left common iliac vein, measuring approximately 4 cm and 4.5 cm in length, respectively, are visible in the coronal plane (**E**). The yellow arrows indicate the locations of the thrombi.

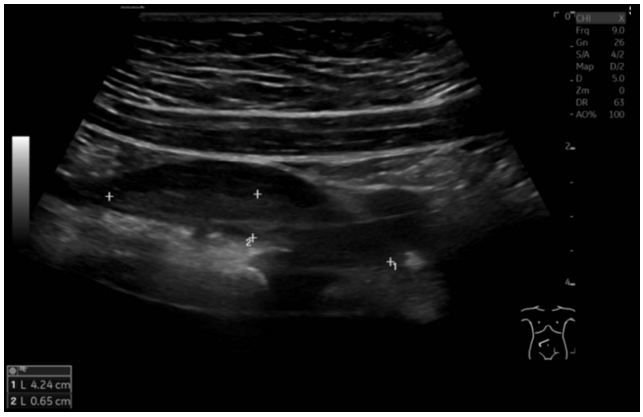

Figure 2 Ultrasound imaging showed a thrombus in the distal end of the inferior vena cava extending to the left common iliac vein (size 4.24×0.65 cm).

be treated with anti-infective therapy. Follow-up ultrasonographic surveillance showed that the deep venous thrombosis had not reformed.

Further investigations were undertaken to investigate the cause of thrombosis. Initial assessment revealed negative lupus anticoagulant and elevated levels of anticardiolipin antibody of IgM and anti-beta2 glycoprotein I (aβ2GPI) IgM. The reevaluation conducted after 10 days showed a negative result for the anticardiolipin antibody of IgM, and the level of aβ2GPI IgM also decreased. An autoantibody profile, including antinuclear antibody, anti-dsDNA, rheumatoid factor, and anti-neutrophil cytoplasmic antibody, yielded negative results. The lab examinations showed normal levels of antithrombin III, protein C, and protein S. The activity of A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13 (ADAMTS-13) was 100%, and antibodies against ADAMTS-13 were not detectable.

After 17 days of hospitalization, the patient's general condition improved. He was discharged on oral rivaroxaban for 3 months. During follow-up visits, the patient remained well with no residual symptoms. The patient underwent the inferior vena cava filter retrieval after 1 month. A repeat chest CT scan performed 3 months later showed resolution of the necrotizing pneumonia.

Discussion

In this case, we have reported an 8-year-old boy who was hospitalized for necrotizing pneumonia, pulmonary artery embolism, and massive thrombi in deep veins due to macrolide-resistant *M. pneumoniae* with a high level of D-dimer and transiently increased anti-phospholipid antibodies. After comprehensive therapies involving anti-infection, anti-inflammatory, and anticoagulation, the massive thrombi were not attenuated. The patient thus underwent inferior vena cava filter placement and catheter-directed thrombolysis with alteplase. The patient ultimately had a favorable prognosis and remained asymptomatic at follow-up.

In 2023, an outbreak of macrolide-resistant *M. pneumoniae* infection occurred in China.[1] The ineffectiveness of conventional therapy may lead to severe pulmonary and extrapulmonary complications. Recent studies have indicated the effectiveness of second-line antibiotics, including tetracyclines and fluoroquinolones, based on the prevalence of antimicrobial resistance.[5,6] There are also several other adjunctive therapies available. The anti-inflammatory and immune regulatory effects of glucocorticoids in managing refractory *M. pneumoniae* pneumonia are well-established.[7] Early effective anti-infection treatment and intravenous immunoglobulin may potentially reduce pathogens to avoid excessive immune reactions. Intravenous immunoglobulin also neutralizes pathogenic antibodies.[8] In this case, the initial empirical anti-infective therapy was ineffective, even with the use of low dose corticosteroids. The patient subsequently developed multiple thrombosis, a rare complication of *M. pneumoniae* infection.

Thrombosis is a rare but potentially life-threatening manifestation of *M. pneumoniae* infection. Previous findings highlight the importance of adequate anticoagulation in the management of hypercoagulable patients with *M. pneumoniae* infection.[4] However, the effect of anticoagulation therapy was unsatisfactory in the present case. Anticoagulants such as low molecular weight heparin primarily act by inhibiting thrombin and factor Xa but do not

directly counteract the underlying inflammatory and immunological mechanisms driving thrombogenesis.[9] Beyond that, successful outcomes after thrombolysis treatment have been reported in a few cases.[10,11] Focusing on the management of pulmonary embolism in children, Ross et al published a review article in 2022. The article specified that high-risk pulmonary embolism, characterized by cardiopulmonary arrest, sustained hypotension, or normotension accompanied by signs or symptoms of shock, should be managed with either surgical thrombectomy or systemic thrombolysis.[12] Furthermore, inadequate therapy for severe deep vein thrombosis may leave the patient at risk for postthrombotic syndrome, venous ulceration, and even pulmonary embolism. The American Society of Hematology guidelines for management of venous thromboembolism in children suggest that anticoagulation alone should be used in pediatric patients with symptomatic deep vein thrombosis or pulmonary embolism, and thrombolysis should be critically considered with regard to the bleeding risk.[13] Because of a lack of evidence, there are no specific recommendations for the management of deep vein thrombosis with persistent symptoms despite aggressive anticoagulation therapy.

Thrombolytic agents (for example, urokinase and tissue plasminogen activator) are increasingly used in children with life- or limb-threatening thrombosis.[14] Alteplase is often preferred in pediatrics due to its short half-life. However, the recommended dosing for thrombolysis in children is highly variable; one proposed regimen suggests using alteplase at 0.5 mg/kg/h over 6 hours for a total of 3 mg/kg with a maximum of 100 mg for systemic thrombolysis.[12] Catheter-directed thrombolysis may benefit patients with a long life expectancy and acute thrombosis involving the iliac and proximal femoral veins by reducing the risk of post-thrombotic syndrome.[15] A study have reported that pediatric patients with acute symptomatic proximal deep venous thrombosis within 2 weeks, presenting a significant clot burden and no elevated risk of bleeding, should be considered for catheter-directed thrombolysis.[16] In our case, initial treatment was conservative. Although he was hemodynamically stable, he experienced severe symptoms. We decided to perform catheter-directed alteplase infusion after a careful multidisciplinary evaluation. The dosage used in this case reflects standard practice at our institution, where alteplase is given at 0.1–0.6 mg/kg/h over 6 hours for arterial embolism or severe thromboembolic events. Vital signs and coagulation status were closely monitored. This approach aligns with dosing recommendations by Ross et al.[12] For safety, no additional continuous alteplase infusion was administered after surgery. The indications for thrombolysis, especially catheter-directed thrombolysis, are not well clarified in patients with pulmonary embolism and deep vein thrombosis due to *M. pneumoniae* infection. Future trials should investigate the use of thrombolysis therapy to promote faster recovery of the lungs and the organs or tissues outside the lungs.

Infection can cause excessive inflammation and dysregulated coagulation. Leukocytes, platelets, and vascular endothelial cells play key roles in the thrombo-inflammation responding in concert to eradicate the invading pathogen.[17] Most studies focus on the thrombo-inflammatory responses in sepsis, where responses are activated by various signals such as toll-like receptor Fcγ-receptors, G protein-coupled receptors, and adhesion receptors on the immune cells.[18] However, the mechanism underlying thrombosis due to *M. pneumoniae* infection remains unclear. Accepted mechanisms of thrombosis include the direct damage to vascular endothelial cells by cytokines and chemokines and indirect damage leading to systemic hypercoagulability.[19] Besides, the transient antiphospholipid antibodies associated with infections react against proteins that bind to phospholipids on plasma membranes, contributing to thrombosis, though their pathogenic role is uncertain.[20,21] Autoimmune modulations have been implicated as a type of indirect damage from *M. pneumoniae* infection,[22] potentially linked to the presence of autoantibodies resulting from molecular mimicry.[23] These autoantibodies lead to an endotype similar to antiphospholipid syndrome and act as critical prothrombotic factors. Similar to our case, transiently elevated levels of anti-phospholipid antibodies were found in patients infected with *M. pneumoniae*. Most patients did not have a defined genetic basis for thrombophilia.[24] These findings suggest that infection-induced mechanisms, rather than genetic factors, play a critical role in thrombogenesis. Exploring the molecular drivers of thrombo-inflammation and immunothrombosis may offer promising targets for future therapeutic interventions.

Conclusion

Comprehensive therapies, including anti-infection, anti-inflammatory, anticoagulation, and thrombolysis, have successfully resolved necrotizing pneumonia and massive venous thrombi induced by macrolide-resistant *M. pneumoniae* infection in a child. Once refractory deep vein thrombosis occurs, the thrombolytic therapy combined with an inferior

vena cava filter could be a promising treatment approach. More indicators should be explored to clarify the specific mechanisms and to guide treatment decisions.

Abbreviations

M. pneumoniae, Mycoplasma pneumoniae; CT, Computed tomography; aβ2GPI, anti-beta2 glycoprotein I; ADAMTS-13, A disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13.

Ethical Approval

According to the institutional policy, ethical approval is required for studies involving patient data. Consent for conducting the study and publishing the case was obtained from the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine (Approval notice number: 2023-IRB-0176-P-01). Written informed consent was obtained from the patient's immediate family member regarding the publication of any potentially identifiable images or data included in this case report.

Disclosure

The authors declare that they have no competing interests.

References

1. Li H, Li S, Yang H, Chen Z, Zhou Z. Resurgence of Mycoplasma pneumonia by macrolide-resistant epidemic clones in China. *Lancet Microbe*. 2024;2623:S2666–5247. doi:10.1016/S2666-5247(23)00405-6
2. Edens C, Clopper BR, DeVies J, et al. Notes from the field: reemergence of Mycoplasma pneumoniae infections in children and adolescents after the COVID-19 pandemic, United States, 2018–2024. *MMWR*. 2024;73(7):149. doi:10.15585/mmwr.mm7307a3
3. Biagi C, Cavallo A, Rocca A, et al. Pulmonary and extrapulmonary manifestations in hospitalized children with Mycoplasma pneumoniae infection. *Microorganisms*. 2021;9(12):2553. doi:10.3390/microorganisms9122553
4. Chen L, Yin J, Liu X, Liu J, Xu B, Shen K. Thromboembolic complications of Mycoplasma pneumoniae pneumonia in children. *Clin Resp J*. 2023;17(3):187–196. doi:10.1111/crj.13584
5. Lee H, Choi YY, Sohn YJ, et al. Clinical efficacy of doxycycline for treatment of macrolide-resistant Mycoplasma pneumoniae pneumonia in children. *Antibiotics*. 2021;10(2):192. doi:10.3390/antibiotics10020192
6. Dai F, Liu F, Chen X, Yang J, Wang K, Guo C. The treatment of macrolide-resistant Mycoplasma pneumoniae pneumonia in children. *J Clin Pharm Therapeut*. 2021;46(3):705–710. doi:10.1111/jcpt.13331
7. Wang Y, Zhou Y, Bai G, et al. Expert consensus on the diagnosis and treatment of macrolide-resistant Mycoplasma pneumoniae pneumonia in children. *World J Pediatr*. 2024;20:901–914. doi:10.1007/s12519-024-00831-0
8. Liu X, Cao W, Li T. High-dose intravenous immunoglobulins in the treatment of severe acute viral pneumonia: the known mechanisms and clinical effects. *Front Immunol*. 2020;11:537006 doi:10.3389/fimmu.2020.01660.
9. Dabbous MK, Sakr FR, Malaeb DN. Anticoagulant therapy in pediatrics. *J Basic Clin Pharma*. 2014;5(2):27. doi:10.4103/0976-0105.134947
10. Song S, Xu Y. A retrospective study of the clinical characteristics of 9 children with pulmonary embolism associated with Mycoplasma pneumoniae pneumonia. *BMC Pediatric*. 2023;23(1):370. doi:10.1186/s12887-023-04188-7
11. Fu Y, Zhang T, Dong C, Xu Y, Dong H, Ning J. Clinical characteristics of 14 pediatric Mycoplasma pneumoniae pneumonia associated thrombosis: a retrospective study. *BMC Cardiovascular Disorders*. 2023;23(1):1. doi:10.1186/s12872-022-03030-9
12. Ross C, Kumar R, Pelland-Marcotte M-C, et al. Acute management of high-risk and intermediate-risk pulmonary embolism in children: a review. *Chest*. 2022;161(3):791–802. doi:10.1016/j.chest.2021.09.019
13. Monagle P, Cuello CA, Augustine C, et al. American society of hematology 2018 guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv*. 2018;2(22):3292–3316. doi:10.1182/bloodadvances.2018024786
14. Navanandan N, Stein J, Mistry RD. Pulmonary embolism in children. *Pediatric Emerg Care*. 2019;35(2):143–151. doi:10.1097/PEC.0000000000001730
15. Fleck D, Albadawi H, Shamoun F, Knuttinen G, Naidu S, Oklu R. Catheter-directed thrombolysis of deep vein thrombosis: literature review and practice considerations. *Cardio Diagn Ther*. 2017;7(Suppl 3):S228. doi:10.21037/cdt.2017.09.15
16. Darbari DS, Desai D, Arnaldez F, et al. Safety and efficacy of catheter directed thrombolysis in children with deep venous thrombosis. *Br. J. Haematol*. 2012;159(3):376–378. doi:10.1111/bjh.12025
17. Iba T, Levy J. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J Thromb Haemost*. 2018;16(2):231–241. doi:10.1111/jth.13911
18. Iba T, Levi M, Levy JH. Intracellular communication and immunothrombosis in sepsis. *J Thromb Haemost*. 2022;20(11):2475–2484. doi:10.1111/jth.15852
19. Hu J, Ye Y, Chen X, Xiong L, Xie W, Liu P. Insight into the pathogenic mechanism of Mycoplasma pneumoniae. *Current Microbio*. 2023;80(1):14. doi:10.1007/s00284-022-03103-0
20. Asherson R, Cervera R. Antiphospholipid antibodies and infections. *Ann Rheumatic Dis*. 2003;62(5):388–393. doi:10.1136/ard.62.5.388
21. Flateau C, Asfalou I, Deman AL, et al. Aortic thrombus and multiple embolisms during a Mycoplasma pneumoniae infection. *Infection*. 2013;41(4):867–873. doi:10.1007/s15010-013-0475-2

22. Narita M. Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia. *J Infect Chemother*. 2010;16(3):162–169. doi:10.1007/s10156-010-0044-X
23. Waites KB, Talkington DF. Mycoplasma pneumoniae and its role as a human pathogen. *Clin Microbiol Rev*. 2004;17(4):697–728. doi:10.1128/CMR.17.4.697-728.2004
24. Liu J, He R, Wu R, et al. Mycoplasma pneumoniae pneumonia associated thrombosis at Beijing Children's hospital. *BMC Infectious Diseases*. 2020;20:1–10. doi:10.1186/s12879-020-4774-9