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# A rare case of multiple thromboses in a pediatric patient with *Mycoplasma pneumoniae* infection

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## ABSTRACT

Medical literature discusses the immunogenicity of *Mycoplasma pneumoniae* and the capability of this bacteria to increase the risk of thrombosis-related events. We present the case of a two-year-old female patient, unvaccinated, with a recent measles infection, who is admitted to the hospital for fever and dyspnea. Serological screening discovered a Mycoplasma infection, paired with the imagistic proof of multiple deep vein thromboses. The evolution was favorable after treatment.

**Keywords:** *Mycoplasma pneumoniae,* systemic inflammation, thromboses

## INTRODUCTION

*Mycoplasma pneumoniae* is one of the smallest pathogens, but it may lead to many community-acquired pneumonia cases in children (10-40% of pneumonia cases) [1].

The course of *Mycoplasma pneumoniae* infection is mainly influenced by the host's defense response to the bacteria, with a sometimes exaggerated pro-inflammatory status, which may result in lung injury, cardiac manifestations, renal injury, hepatitis, and last but not least, thrombosis [2-4].

Generally, the course of *Mycoplasma pneumoniae* infections is self-limited, with a favorable outcome. There are reported cases of "walking pneumonia", in which patients accuse only a lingering productive cough and fatigability, which is inconsistent with the radiological aspects [5,6]. The imaging of this atypical pneumonia usually suggests unilateral or bilateral lower pulmonary lobe implications [7].

But the particular immunogenicity of *Mycoplasma pneumoniae* induces signals that kick-start the conglomeration of inflammatory cytokines, specifically IL-1, IL-8, and TNF-a[8], which overlaps the host defense mechanisms and plays a vital role in the development of immunothrombosis (a coagulopathy generally associated with systemic inflammation, sepsis).

## CASE DESCRIPTION

A 2-year-old female patient presented in the Emergency Room at Brasov Clinical Hospital for fever bouts (a maximal value of 39.6°C) that started seven days before presentation, accompanied by debilitating cough and dyspnea.

The girl was born at term with no obstetrical events worth mentioning. The immunization schedule is incomplete (the last vaccine was the hexavalent one at four months old).

The patient's medical history consists of one hospital admission in October of 2023 for bacterial pneumonia. The patient received 100 mg/kg/day of ceftriaxone IV for three days during that hospital admission. Afterward, she exhibited monthly respiratory manifestations, mainly a debilitating productive cough, that led to visits to the local general practitioner and repeated antibiotic treatment at home. The patient had measles recently, which was also treated at home.

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The clinical state of the patient at the present hospital admission is critical. She exhibits debilitating bouts of dry, irritative cough, expiratory dyspnea, pulmonary bilateral crackles, sat02-80% without administered oxygen, and tachycardic (HR=170 bpm). She has an average weight for her age (12.5 kg, P48th).

The thoracic X-ray describes bronchopneumonia (Figure 1).

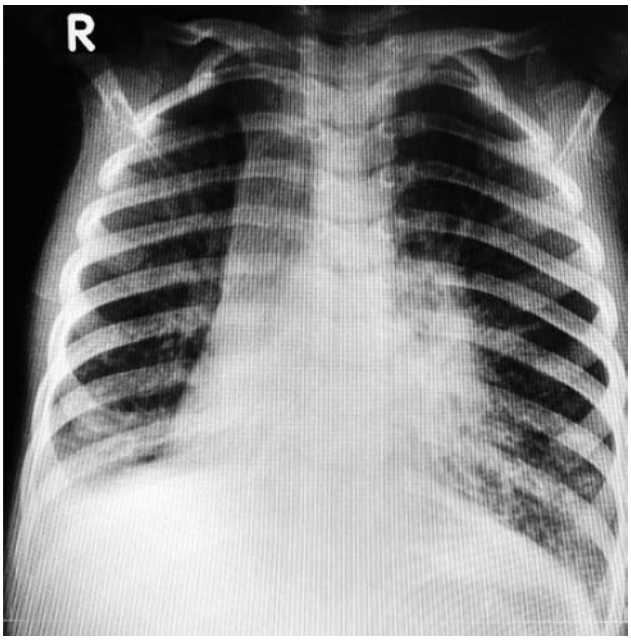


**FIGURE 1.** Thoracic X-ray

Laboratory tests reveal accentuated inflammatory syndrome, with high levels of white blood cell count 29720/mm$^3$ (normal values: 4,500-11,000/mL), CRP 8 mg/dl (normal value <1 mg/dL), ESH 65 mm/h, (normal values: 0-10 mm/h) and procalcitonin 1 ng/ml (normal values <0.5 ng/mL) along with elevated levels of D-dimers 6 ng/ml (normal values <0.5 ng/mL). Treatment was started with ceftriaxone 100 mg/kg/day IV, vancomycin 60 mg/kg/day IV, methylprednisolone 4 mg/kg/day IV, 4 liters of oxygen flow on mask, intravenous drips with glucose and electrolytes.

On the first night of hospitalization, the patient exhibited a tonic seizure, with the sudden installment of a generalized maintained contraction, eyes rolled back, and oxygen saturation levels decreased down to 50%, all of which lasted 30-50 seconds. The return to consciousness was not followed by post-ictal sleepiness. Immediately after the neurologic manifestation, laboratory tests showed severe metabolic acidosis (pH=6.9, $pCO_2$ 71 mmol/L, $HCO_3$ 13.5 mmol/L), which normalized in one hour without medication.

Another thoracic x-ray was performed because the respiratory distress did not alleviate after treatment, and more pulmonary consolidations were described.

The cerebral CT scan (Figure 2) reveals right sinus and transverse sinus thrombosis, and the thoracic CT scan describes major bilateral lower lobes bronchiectases, much more accentuated on the right lower lobe (Figure 3).

The serological PCR method screening results returned positive for IgM antibodies and titers for *Mycoplasma pneumoniae.*

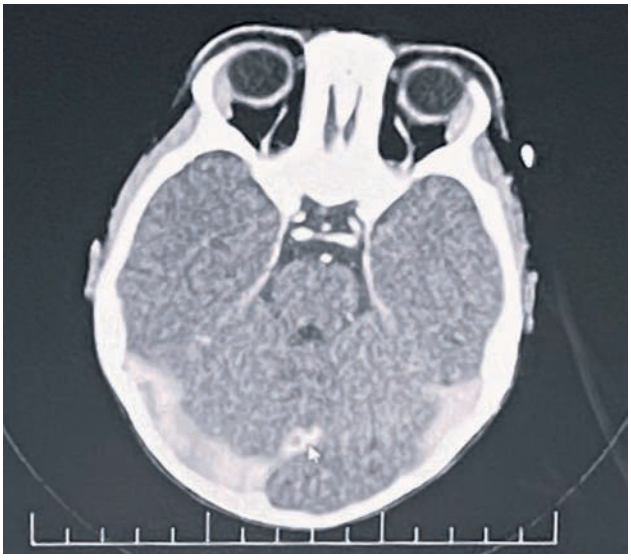

**FIGURE 2.** Cerebral CT scan

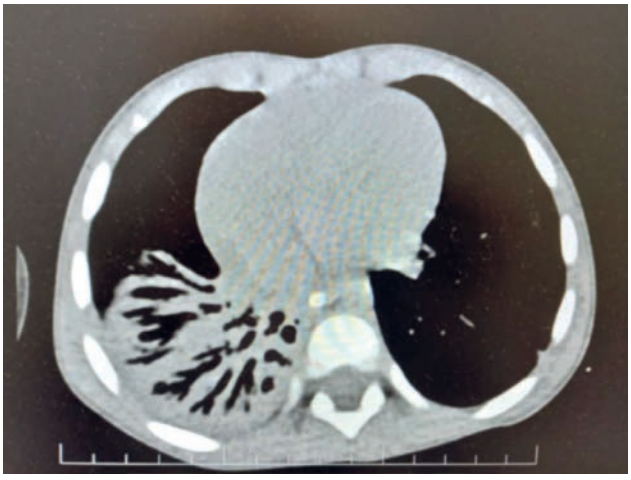

**FIGURE 3.** Thoracic CT scan

The patient presented more seizures in the following days that lasted longer (5 minutes each), with axial contracture, rolled back eyes, and severe desaturations that did not respond to phenobarbital administration. The association of valproic acid does not prevent neurological manifestations.

She was transferred to the Intensive Care Unit, where she presented cardiopulmonary arrest when she received subsequent doses of adrenaline 0.01 mg/kg IV along with oro-tracheal intubation and careful monitoring until the normalization of heart rate, blood pressure, and oxygen saturation levels. The medication scheme was modified, with the re-

placement of Ceftriaxone with Meropenem IV (100 mg/kg/day), the association of Caspofungin IV (50 mg/m$^2$) and Aciclovir IV (750 mg/day-500 mg/m2), clarithromycin po (15 mg/kg/day) and the continuation of methylprednisolone (dose was reduced to 2 mg/kg/day for a total of 13 days).

An angio-CT scan (Figure 4) was performed, and another thrombosis site was discovered: pulmonary thromboembolism at the right posterior segmental pulmonary artery and the middle lobar artery.

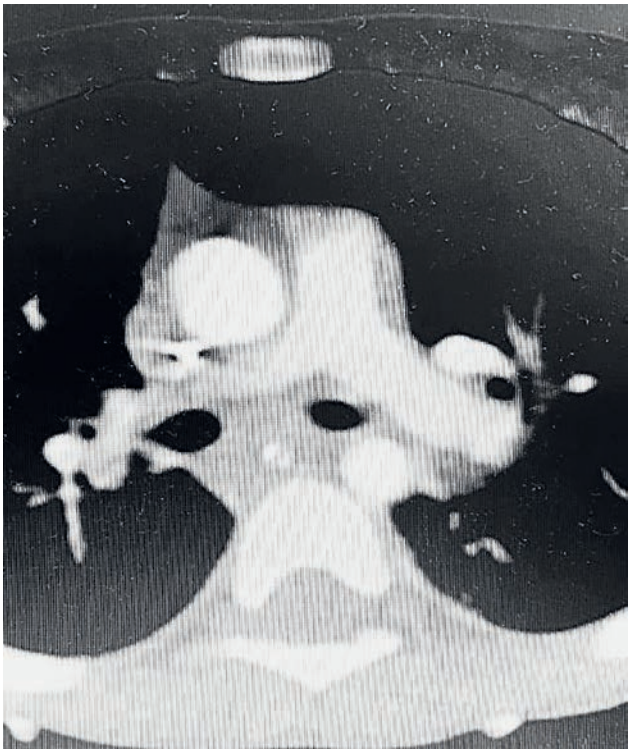

**FIGURE 4.** Angio CT scan

A low molecular weight heparin anticoagulant was associated with the treatment, and she was successfully extubated after three days, with a complete regain of consciousness, no apparent neurological sequelae, and no subsequent seizures.

A race to find thrombosis etiology began. Normal values of protein C and S were found, negative antiphospholipid antibodies were found, and the genetic profile for thrombophilia did not meet the required criteria to diagnose hereditary thrombophilia.

The patient did not have a positive history of seizures or other thrombosis events pre-hospital admission that could justify a preexisting condition.

She also did not present malnutrition or modified levels of pancreatic elastase levels that could explain the presence of bronchiectasis to cystic fibrosis.

Therefore, this patient's clinical and paraclinical manifestations were attributed to the systemic inflammation associated with *Mycoplasma pneumoniae* in a non-vaccinated host with depleted resources after a recent measles episode. The high procalcitonin value and the positive *Mycoplasma pneumoniae* PCR serology confirmed the septical dissemination. A cerebral RMN and a thoracic angio-CT scan were performed to reassess the situation of deep thromboses after three weeks of treatment. Cerebral vein thromboses visibly decreased, while there were no evident alterations in the size of the pulmonary artery thrombosis.

After 24 days of hospitalization, the patient was discharged with a good general state, Glasgow Coma Scale of 15, no seizures or neurological sequelae, residual cough, normal oxygen saturation levels, no pulmonary crackles, and normal heartbeat rate. Laboratory tests at discharge reveal normochromic normocytic moderate anemia (Hb=8 g/dl, probably in the acute infectious context), normal values of WBC, CRP, ESH, procalcitonin, D dimers value halved than the one at admission (3 pg/ml).

The mother was educated on the necessity of the correct administration of enoxaparin injections, and the patient continued with enoxaparin 2000 ui/vial - 0.15 mg twice a day subcutaneously. The use of other anticoagulant medications was discussed (factor X inhibitors-dabigatran, or coumarin derivates-acenocoumarol), but because of practical reasons, enoxaparin was elected. After being discharged, the patient came back twice a month for clinical re-evaluation, along with periodic re-assessment of main laboratory tests (complete blood count, inflammatory syndrome markers-CRP, ESH, seric urea, and creatinine, AST, ALT, D-dimers, fibrinogen-all of them with no notable alterations).

## DISCUSSION

Inflammation is the host's natural and necessary response in defending against a pathogen factor. There is an increase in blood flow to facilitate the conglomeration of inflammatory mediators. Activated neutrophils release pro-inflammatory and pro-thrombotic factors that, along with the endothelial wall dysregulation, sometimes lead to immunothrombosis [9].

Another critical factor in sepsis-related thrombosis is the aggregation of platelets in the regions with endothelial wall injury. The platelets generate signals that kick-start the hemostasis process with the sole purpose of wound healing, but unfortunately, these processes are amplified in sepsis [10].

Pairing all of the above with the characteristic immunogenicity of *Mycoplasma pneumoniae* increases the risk of thrombosis-related events even more [11, 12, 13, 14].

Although hematological manifestations in *Mycoplasma pneumonia* are viewed as relatively uncom-

mon events, the development of profound venous thrombosis is possible because Mycoplasma is an intracellular pathogen and has direct cytotoxicity, inducing the activation of the inflammatory cascade, as well as a consequence of the hypercoagulability state that derives from systemic inflammations [15]. Medical literature describes one case of profound venous thrombosis in a patient with *Mycoplasma pneumoniae* infection that showed no respiratory manifestations [15].

Medical literature also describes the presence of deep venous thrombosis in patients who did not have a congenital predisposition for this type of hematological malfunction but were only secondary to infection with *Mycoplasma pneumoniae* [16,17].

The particularity of this case stems from the dramatic clinical course of an unvaccinated two-year-old who recently recovered from measles, with probably weakened immunity resources to fight a systemic inflammation caused by *Mycoplasma pneumoniae.* This resulted in multiple deep vein thromboses in a child without hereditary thrombophilia or any other found hereditary blood coagulation abnormality.

Another important entity worth discussing is the hematological sequelae – chronic pulmonary thromboembolism, which requires chronic anticoagulant use. The patient is to receive three months of enoxaparin with bimonthly clinical re-evaluation for active hemorrhages [18].

## CONCLUSIONS

In the presented case, several factors were involved that finally led to the development of multiple thromboses—a vulnerable, unvaccinated pediatric host with a recent history of measles infection who developed an aggressive inflammatory response to a bacteria that is already associated with the possibility of inducing hematological manifestations by its direct cytotoxicity.

The data from medical literature, correlated with our clinical and paraclinical findings, highlight the idea that assessing the extra-pulmonary complications, especially thrombosis, is always essential in a patient with severe, disseminated *Mycoplasma pneumonia* infection. This article aims to draw attention to the complications that may arise in a *Mycoplasma pneumoniae* infection in the pediatric population, especially in the 0-5 year old age group.

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## REFERENCES

1. Lee KY. Pediatric respiratory infections by Mycoplasma pneumoniae. Expert Rev Anti Infect Ther. 2008;6:509–521.
2. Shimizu T, Kida Y, Kuwano K. Cytoadherence-dependent induction of inflammatory responses by Mycoplasma pneumoniae. *Immunology.* 2011;133:51-61. http://doi.org/10.1111/j.1365-2567.2011.03408.x
3. Narita M. Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia. *J Infect Chemother.* 2010;16:162-9. http://doi.org/10.1007/s10156-010-0044-x
4. Youn YS, Lee KY. Mycoplasma pneumoniae pneumonia in children. *Korean J Pediatr.* 2012 Feb;55(2):42-7. http://doi.org/10.3345/kjp.2012.55.2.42. Epub 2012 Feb 14. PMID: 22375148; PMCID: PMC328676
5. Baum SG, Goldman DL. Mycoplasma infections. In: Goldman L, Schafer AI, eds. Goldman-Cecil Medicine. 26th ed. Philadelphia, PA: Elsevier; 2020:chap 301.
6. Holzman RS, Simberkoff MS, Leaf HL. Mycoplasma pneumoniae and atypical pneumonia. In: Bennett JE, Dolin R, Blaser MJ, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 9th ed. Philadelphia, PA: Elsevier; 2020:chap 183.
7. John SD, Ramanathan J, Swischuk LE. Spectrum of clinical and radiographic findings in pediatric mycoplasma pneumonia. *Radiographics.* 2001;21(1):121-31. http://doi.org/10.1148/radiographics.21.1.g01ja10121
8. Yang J, Hooper WC, Phillips DJ, Talkington DF. Cytokines in Mycoplasma pneumoniae infections. *Cytokine Growth Factor Rev.* 2004;15:157-68. http://doi.org/10.1016/j.cytogfr.2004.01.001
9. Marcos-Jubilar M, Lecumberri R, Páramo JA. Immunothrombosis: Molecular Aspects and New Therapeutic Perspectives. *J Clin Med.* 2023 Feb 9;12(4):1399. http://doi.org/10.3390/jcm12041399. PMID: 36835934; PMCID: PMC9958829
10. Iba T, Levi M, Levy JH. Intracellular communication and immunothrombosis in sepsis. *J Thromb Haemost.* 2022 Nov;20(11):2475-2484. http://doi.org/10.1111/jth.15852. Epub 2022 Aug 28. PMID: 35979601; PMCID: PMC9804233.
11. Chen L, Yin J, Liu X, Liu J, Xu B, Shen K. Thromboembolic complications of Mycoplasma pneumoniae pneumonia in children. *Clin Respir J.* 2023 Mar;17(3):187-96. http://doi.org/10.1111/crj.13584. Epub 2023 Jan 19. PMID: 36658687; PMCID: PMC9978901.
12. Fu Y, Zhang TQ, Dong CJ, Xu YS, Dong HQ, Ning J. Clinical characteristics of 14 pediatric mycoplasma pneumoniae pneumonia associated thrombosis: a retrospective study. *BMC Cardiovasc Disord.* 2023 Jan 4;23(1):1. http://doi.org/10.1186/s12872-022-03030-9. PMID: 36600223; PMCID: PMC9811738.
13. Chen S, Ke S, Vinturache A, Dong X, Ding G. Pulmonary embolism associated with Mycoplasma pneumoniae pneumonia in children. *Pediatr Pulmonol.* 2023;58:3605-8. http://doi.org/10.1002/ppul.26691
14. Zhang T, Zheng J, Wang H, Xu Y, Ning J, and Cai C. Case Report: Cardiac Multiple Thrombus and Pulmonary Embolism Associated With Mycoplasma Pneumonia Infection in a Child. *Front Pediatr.* 2022;10:959218. http://doi.org/10.3389/fped.2022.959218
15. Mirijello A, La Marca A, D'Errico MM, Curci S, Vendemiale G, Grandone E, et al. Venous Thromboembolism During Mycoplasma Pneumoniae Infection: Case Report and Review of the Literature. *Eur Rev Med Pharmacol Sci.* 2020;24(19):10061-8. http://doi.org/10.26355/eurrev_202010_23223
16. Van Dyke DC, Eldadah MK, Bale JF Jr, Kramer M, Alexander R, Smith WL, Olivero W. Mycoplasma pneumoniae-induced cerebral venous thrombosis treated with urokinase. *Clin Pediatr (Phila).* 1992;31:501-4.
17. Miragliotta G, Fumarola D. Intravascular coagulation and Mycoplasma pneumoniae infection. *Lancet.* 1988;1:243. http://doi.org/10.1016/s0140-6736(88)91095-1
18. Mendoza V, Scharf ML. Evaluation and management of chronic pulmonary thromboembolic disease. *Hosp Pract* (1995). 2011 Aug;39(3):50-61. http://doi.org/10.3810/hp.2011.08.580. PMID: 21881392