Stroke in *Mycoplasma pneumoniae* pneumonia: a case report

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Abstract

Mycoplasma pneumoniae (MP) cause more than 40% of community-acquired pneumonia. Sometimes extrapulmonary manifestations may occur: in particular, central nervous system (CNS) symptoms occur in 10% of hospitalizations for MP. A young woman was being admitted to our intensive care unit (ICU) for respiratory failure and suspected stroke, ten days after flu-like syndrome. The patient was already intubated, sedated, in controlled mechanical ventilation. At admission brain computed tomography (CT) was negative, chest CT showed bilateral pneumonia with interstitial thickening. After 36 hours, brain CT showed an extensive hypodense cortico-subcortical area with frontal-parietal-temporal left seat. The positivity of IgM for MP and PCR in nasopharynx led to the diagnosis of MP pneumonia complicated by stroke: 15 days after admission, a post-ischemic status was manifested by aphasia, dysphagia, right brachio-crural hemiplegia. In our paper we evaluated possible major neurological complications, up to stroke, in MP respiratory infection. We concluded that, although they are actually rare, neurological symptoms up to cerebral ischemia in young people with MP pneumonia, are to be considered.

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Introduction

Mycoplasma pneumoniae (MP) cause more than 40% of community-acquired pneumonia (CAP), affecting pediatric and young adult age at a higher frequency. These are usually mild and self-limiting lung infections, that sometimes appear to be asymptomatic.[1,2]

The infection can induce respiratory system involvement, including tracheobronchitis and coughing, as well as more serious symptoms like pneumonia. A dry cough typically begins during the acute phase of an infection and might escalate to coughing up phlegm in 3-4 days. The most frequent type of infection is tracheobronchitis, which causes coughing.[3] In most cases, chest auscultation is not helpful in making a diagnosis, but scattered rhonchi and wheezing may occur.[4] If the situation worsens, pneumonia may emerge; atypical pneumonia is one of the most common disorders in adults. In the progressive forms, pharyngitis, sinus congestion, occasionally otitis media, and finally protracted involvement of the lower respiratory tract up to pneumonia, with low-grade fever and bibasilar pulmonary infiltrates, are common. Dry rales with a frank consolidation may be present in severe pneumonia, but this is quite rare.[4,5]

At the laboratory, there may be modest leukocytosis, but the total white blood cell count rarely exceeds 15,000/L. Because MP is tiny and lacks a cell wall, sputum is not viscous and does not take a Gram stain.[3] Air-space opacification, bronchovascular thickening, atelectasis, nodular infiltration, and linear opacities outward from the hilum are the most common radiological and high resolution computed tomography (CT) images of MP pneumonia (they are actually indistinguishable from other bacterial or viral pneumonia patterns).[6,7]

A lightning-fast presentation with acute respiratory distress syndrome (ARDS) or diffuse alveolar bleeding has been reported. As for extra-pulmonary manifestations, MP can involve any organ, whether as a direct expression of the infectious process, or as autoimmune or vascular complications.

The involvement of the central nervous system (CNS) is undoubtedly the most widespread among extra-pulmonary charac-

teristics, occurring until the 10% of patients with MP infection confirmed serum that requires hospitalization.[8]

Neurological pictures range from meningoencephalitis to optic neuritis, transverse myelitis to stroke, and appears shortly after MP infection, especially in the younger population. Vascular lesions can further lead to striatal necrosis and psychological disorders; peripheral nerve involvement, cranial nerve paralysis and Guillain-Barré paralysis may also occur.[9]

A large prospective study available in literature, would show that patients with recent MP infection might have a higher risk of ischemic stroke rather than controls combined with comorbidity over a 5-year follow-up period.[10]

These findings imply that MP may be able to raise the risk of ischemic cerebrovascular accident even over a long period of time, through a variety of pathways.[11] The clinical example mentioned in our paper demonstrates the link between MP infection and stroke. Our current understanding of this uncommon but potentially fatal cause of cerebral infarction is limited. The goal of this paper is to provide a suggestive clinical case while analysing the probable pathogenetic pathways studied in the literature.

Case Report

The patient was a 40-year-old female patient with a positive history of migraine and tobacco habit. She presented a slight excess of weight, and worked as an employee in the catering industry.

For the advent of flu-like symptoms, cough, and fever, the family doctor advised empirical therapy with oral amoxicillin/clavulanate and betamethasone: since there was no significant improvement after 9 days, he added oral ciprofloxacin. However, on the tenth day, the clinical picture became more complicated with the onset of neurological disorders such as difficulty walking and hyposthenia in the right upper limb, it became more serious in the following 24 hours when the patient experienced space-temporal disorientation and difficulty breathing. The patient appeared soporous (GCS not mentioned in other structure) and in respiratory distress with right hemiparesis when rescued by the prehospital unit and transferred to the emergency room (ER). The brain CT and thoraxd angiotc performed in an emergency did not reveal any acute brain lesions, but there were many areas of bronchioalveolar thickening with significant accentuation of the interstitium, as well as thickening bilateral basal parenchymal. The arterial blood gas (ABG) exam revealed respiratory alkalosis with severe hypoxemia, as well as notable neutrophil leucocytosis, platelets, PCR, and D dimer increases. The right brachiocrural hyposthenia continued. The patient was admitted to our hospital's intensive care unit (ICU) after undergoing orotracheal intubation and controlled mechanical ventilation. Our department confirmed acute respiratory failure, but the prolonged analgosedation prevented us from assessing the patient's neurological health. This was followed by mechanical breathing at high FiO_2 and continuous sedation with midazolam and fentanyl.

The admission laboratory test showed white blood cells 31.4 10^{3}/mm ^{3} of which 24.84 neutrophils and 4.02 lymphocytes, platelets 701,000 (v.n. 142,000-424,000), LDH 1372 (v.n. 240-480), PCR 6.7 (v.n. 0-0.5) and procalcitonin 0.1. The patient was subjected to two sets of blood cultures, urinary Ag research of *Legionella pneumophila*, research of Ab micoplasma pneumonia, bronchcoaspirate for common germs from endotracheal tube, nasopharyngeal buffer for research of respiratory pathogens by PCR.

At the admission, a broad-spectrum empirical therapy was set with intravenous linezolid 600 mg × 2/day, meropenem 1 gr × 3/day, ciprofloxacin 400 mg × 2/day. It was decided to proceed with steroid therapy with methylprednisolone intravenous. After 24 hours, the research of antibodies against Mycoplasm with chromatographic method provided a positive result, confirmed by the discovery of mycoplasma DNA by PCR on nasopharyngeal buffer. Based on cultures, the antibiotic scheme was modified suspending the carbapenem and adding intravenous clarithromycin 500 mg × 2/day.[12] Meanwhile, at 36 hours from the admission, the patient was subjected to a new brain and thorax CT scan that showed in the brain the appearance of an extensive cortico-subcortical hypodense area in the left frontal-parieto-temporal with mass effect on the lateral ventricle homolateral and minimum shift of the midline; flogistic material was found in the maxillary sinuses and ethmoil cells; in the pulmonary area were observed thickening parenchymal with aerial broncogram to the basal segments bilaterally and circumscribed frosted glass areas spread on both sides. Lysine acetysalicylate 300 mg was added in therapy and, on the indication of the neurologist, antiedema therapy was set with mannitol 100 mg × 3/day for the next 48 hours. On the fourth day, analgosedation was withhold with gradual recovery of the patient to the vigilance and responsiveness to painful stimulus from the left hemilateral, persisting hemiplegia to the right hemilateral. The weaning was then started by mechanical ventilation, with estubation protected on the sixth day and initial non invasive ventilation in oronasal mask in the following 24 hours in support pressure. At the neurological assessment, the patient appeared alert, however aphasia was evidenced with greater impairment of the expressive component, apraxia bucco-lingual; severe right hemiparesis was confirmed with upper plegic limb and lower paretic limb.

Antibiotic therapy with clarithromycin and ciprofloxacin was continued until the new CT scan control, carried out after about two weeks from the entry in the intensive care unit (ICU) from which a clear improvement seemed to be evident, with parenchymal and interstitial pulmonary picture and a reduction in the size of the large fronto-temporo-parietal hypodense area. After a little more than two weeks from hospitalization, the general conditions were improved, as were the gas exchanges at ABG and laboratory tests, with normalization of the blood count and a sharp reduction in the index of inlammation. She continued her therapy with ASA and passive mobilization. Therefore, the patient with a clear post ischemic status in evolution, characterized by motor aphasia, dysphagia and hemiplegia brachio-crurale right was discarged to highly specialized rehabilitation institute, for the continuation of post-acute care. To date, it appears that the patient, now returned to her home, has partially recovered the use of the upper limb, using a support for walking; the aphasia seems to persist even if she manages to evoke some sounds. She is having her physiotherapy sessions and she feeds herself. She has fully recovered her pulmonary function.

Discussion

The MP colonizes the oropharynx and can subsequently invade the bloodstream and reach the CNS. In case of acute encephalitis or stroke, growth of MP in culture media has been demonstrated after direct sampling of CNS or cerebrospinal fluid tissue.[13,14] Among other things, it can be hypothesized that the spreading in the blood stream of bacteria would act locally on the walls of the cerebral vessels, inducing the release of cytokines and chemokines such as TNFα and IL8: this would determine a vasculitis, a thrombotic vascular occlusion, or both, even in the absence of a hypercoagulative state.[15] Moreover, bacteria or some of their components, once transported through the Blood Brain Barrier, could cause a local

immunological reaction at this level. This mechanism of cell-mediated immunity could at least partly explain the late-onset vasculopathy found in some cases in the literature after 2-3 weeks from the acute respiratory episode by MP.[16,17] Another mechanism of the onset of related cerebrovascular pathology MP could be a state of hypercoagulability induced by surface proteins and chemical mediators produced by the bacteria. MP would induce the release of IL1 and TNF with endothelial activation and alteration of local coagulability and subsequent trigger of an intravasal coagulative cascade in venous or arterial beds. In a large number of patients, as emerged from literature, there would be a condition of thromboembolism that leads precisely to the occlusion of the cerebral artery resulting in a stroke. In our case, for the research of cardioemboligen sources the patient had been subjected to several instrumental investigations: trans-esophageal echocardiogram with evidence of foramen ovale patency[18] with tunnel of about 15×3 mm; the poor compliance of the patient at the time of the examination and the impossibility to perform the Valsalva did not allow to highlight any shunt; supra-aortic doppler US did not identify relevant thrombus; deep venous thrombosis was not found. Finally, coagulation screening showed a very slight deficiency of protein S=54.2% (n.v. 60-140), which is not significant.

An association between MP infection and stroke, particularly in children, is described in the scientific literature. However, our current knowledge about this potential cause of stroke is limited.

In 2003 Sotgiu *et al.* documented 3 cases of young women with a recent respiratory tract infection caused by MP some weeks before the neurological complication. Two patients suffered from demyelinating disorders of the CNS. In the other case, a middle cerebral artery thrombosis was diagnosed, a rare complication of MP infection. The Authors concluded by hypothesizing that recent MP infection represents a risk factor for cerebrovascular disorders and CNS demyelinating diseases.[19] A case very similar to ours was described by Kong *et al.* in a 2012 paper. In this article, a young girl was described with hemiplegia and aphasia following a respiratory infection from MP. The same Authors then proceeded to an interesting review of the literature.[20] In a 2011 work, Chang *et al.* observed 1094 patients with MP infection over a 5-year period compared with 5168 subjects matched for sex, age, and comorbidities but without MP. The Authors highlighted that the risk of ischemic stroke was increased in patients with MP infection.[10] In a 2018 review, Mèlè *et al.* searched PubMed and Embase to identify publications related to stroke occurring within 4 weeks of MP infection. In this review, the authors found 28 cases in which patients ranged in age from newborn to 57 years, with a mean age of 8 years. From the analysis of the works that we took under consideration, the Authors hypothesize that the possible short-term pathogenesis could include hypercoagulability and infection-related vasculitis.[21]

Conclusions

Although CNS manifestations up to cerebral stroke in young patients with respiratory MP infection are a very rare event, such postinfectious neurological complications should not be excluded. Cerebral ischemia associated with MP probably recognizes a multifactorial pathogenesis in which an immune-based hypercoagulable condition and vasculitis could play an important role. Furthermore, we need to understand whether in long term MP infection could represent an independent risk factor for cerebrovascular accident, investigating the possible relationship between MP and atherosclerosis.

References

1. Koskiniemi M. CNS manifestations associated with Mycoplasma pneumoniae infections: summary of cases at the University of Helsinki and review. Clin Infect Dis 1993;17: S52-7.
2. Kolski H, Ford-Jones EL, Richardson S, et al. Etiology of acute childhood encephalitis at The Hospital for Sick Children, Toronto, 1994-1995. Clin Infect Dis 1998;26:398-409.
3. Parrot G.L., Kinjo T and Fujita J. A compendium for mycoplasma pneumonaie. Front Microbiol 2016;7:513.
4. Norisue Y, Tokuda Y, Koizumi M, et al . Phasic characteristics of inspiratory crackles of bacterial and atypical pneumonia. Postgrad Med J 2008;84:432-6.
5. Nambu A, Saito A, Araki T, et al. Chlamydia pneumoniae: comparison with findings of Mycoplasma pneumoniae and Streptococcus pneumoniae at thin-section CT. Radiology 2006;238:330–8.
6. Reittner P, Muller NL, Heyneman L, et al. Mycoplasma pneumoniae pneumonia: radiographic and high-resolution CT features in 28 patients. Am J Roentgenol 2000;174:37–41.
7. Miyashita N, Sugiu T, Kawai Y, et al. Radiographic features of Mycoplasma pneumoniae pneumonia: differential diagnosis and performance timing. BMC Med Imaging 2009;9:7
8. Tsiodras S, Kelesidis I, Kelesidis T, et al. Central nervous system manifestations of Mycoplasma pneumoniae infections. J Infect 2005;51:343-54.
9. Palumbo E, Malorgio C, Nasca G, et al. Encefalite da mycoplasma pneumoniae in un bambino immunocompetente. Recenti Prog Med 2008;99:306-8.
10. Chiang CH, Huang CC, Chan WL, et al. Association between Mycoplasma pneumonia and increased risk of ischemic stroke: a nationwide study. Stroke 2011;42:2940–3.
11. Higuchi ML, Sambiase N, Palomino S, et al. Detection of Mycoplasma pneumoniae and Chlamydia pneumoniae in ruptured atherosclerotic plaques. Braz J Med Biol Res 2000;33: 1023-6.
12. Lu Y-J, Chen T-H, Lin L-H, et al. Macrolide use shortens fever duration in Mycoplasma pneumoniae infection in children: a 2-year experience . J Microbiol Immunol Infect 2008;41:307-10.
13. Socan M, Ravnik I, Bencina D, et al. Neurological symptoms in patients whose cerebrospinal fluid is culture- and/or polymerase chain reaction-positive for Mycoplasma pneumoniae. Clin Infect Dis 2001;32:E31-5.
14. Padovan CS, Pfister HW, Bense S, et al. Detection of Mycoplasma pneumoniae DNA in cerebrospinal fluid of a patient with M. pneumoniae infection-"associated" stroke. J Clin Microbiol 2007;45:2726-30.
15. Bitnun A, Ford-Jones EL, Petric M, et al. Acute childhood encephalitis and Mycoplasma pneumoniae. Clin Infect Dis 2001;32:1674-84.
16. Perez C, Montes M. Cutaneous leukocytoclastic vasculitis and encephalitis associated with Mycoplasma pneumoniae infection. Arch Intern Med 2002;162:352-4.
17. Mirsky DM, Beslow LA, Amlie-Lefond C, et al. Pathways for neuroimaging of childhood stroke. Pediatr Neurol 2017; 69:11-23.
18. Turc G, Calvet D, Guerin P, et al. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. J Am Heart Assoc 2018;7:e008356.

19. Sotgiu S, Pugliatti M, Rosati G, et al. Neurological disorders associated with Mycoplasma pneumoniae infection. Eur J Neurol 2003;10:165-8.
20. Kong M, Jiang L, Hu J, Ye YZ. [Clinical characteristics of Mycoplasma pneumoniae-associated ischemic stroke in children, and a literature review]. Zhongguo Dang Dai Er Ke Za Zhi 2012;14:823-6. Chinese.
21. Mélé N, Turc G. Stroke Associated With Recent Mycoplasma Pneumoniae Infection: A Systematic Review of Clinical Features and Presumed Pathophysiological Mechanisms. Front Neurol 2018;9:1109.