

Refractory *Mycoplasma pneumoniae* pneumonia with concomitant acute cerebral infarction in a child

A case report and literature review

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Abstract

Rationale: *Mycoplasma pneumoniae* pneumonia, a common cause of community-acquired pneumonia in children, is rarely complicated with acute cerebral infarction.

Patient concerns: We present a 7-year-old boy with severe *M pneumoniae* pneumonia who developed impaired consciousness, aphasia, and reduced limb muscle power 7 days postadmission.

Diagnoses: Mycoplasma pneumoniae pneumonia with concomitant acute cerebral infarction.

Interventions: The patient recovered with aggressive antibiotic therapy, antiinflammation therapy with methylprednisolone, and gamma immunoglobulin and anticoagulation therapy with aspirin and low molecular weight heparin along with rehabilitation training.

Outcomes: At 8 days postadmission, his consciousness was improved and at the 6-month follow-up visit, his muscle power of bilateral upper and lower limbs was normal except still poor right handgrip power.

Lessons: Stroke or cerebral infarction should be considered and promptly managed in rare cases of *M pneumoniae* pneumonia with neurologic manifestations.

Abbreviations: MCA = middle cerebral artery, MRA = magnetic resonance angiography.

Keywords: cerebral infarction, diagnosis, pneumonia, stroke, therapy

1. Introduction

Mycoplasma pneumoniae is a common cause of community-acquired pneumonia in children and *M pneumoniae* infection accounts for approximately 20% of pediatric pneumonia patients requiring hospitalization.^[1,2] *M pneumoniae* infection has been reported to cause various neurological complications including aseptic meningitis, transverse myelitis, cerebellar ataxia, Guillain-Barré syndrome,^[3] and encephalopathy,^[4] which is considered to be an immune-mediated response to injury. Ischemic stroke is very uncommon in children with a reported annual incidence rate of only 0.63 per 100,000 population in children under 14 years of age.^[5]

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The estimated incidence of pediatric stroke between 1998 and 2001 was 2.1 cases per 100,000 children-years among children <15 years of age in Hong Kong.^[6] Severe *Mycoplasma pneumoniae* pneumonia with cerebral infarction is clinically rare with a high morbidity and mortality. Liu et al reported^[7] a clinical series of 65 pediatric cases of ischemic stroke and only 1 child had *M pneumoniae* infection-associated ischemic stroke. In the current paper, we report a case of severe *M pneumoniae* pneumonia with concomitant cerebral infarction in a 7-year-old boy. The patient successfully recovered after intensive therapies including treatment with antibiotics, inflammation control with methylprednisolone, anticoagulation therapy with aspirin and heparin, and active rehabilitation training.

2. Case report

A 7-year-old boy was admitted on November 25, 2016 because of fever and cough for 6 days. On November 19, 2016, the boy started having fever for no apparent reason with the highest body temperature at 39.7°C. He also had irritative coughs, which were worsened at late night and early morning. The patient did not complain of other symptoms including respiration difficulties, headache, vomiting, and limited movements (right upper limb muscle power, grade 1; right lower extremity muscle power, grade 1; left upper limb muscle power, grade 3; and left lower extremity muscle power, grade 3). Three days before admission, he received cefdinir (50 mg, twice daily) for 2 days, oral azithromycin (0.2 g/day), and unknown intravenous antibiotics at a local hospital.

His history was unremarkable, with no previous contact with infectious disease. He received all vaccinations as scheduled.

On admission, the boy was mentally oriented. His temperature was 37.0°C, pulse 110/min, and respiration 30/min. The pharynx was congested, and bilateral tonsils were mildly swollen but with

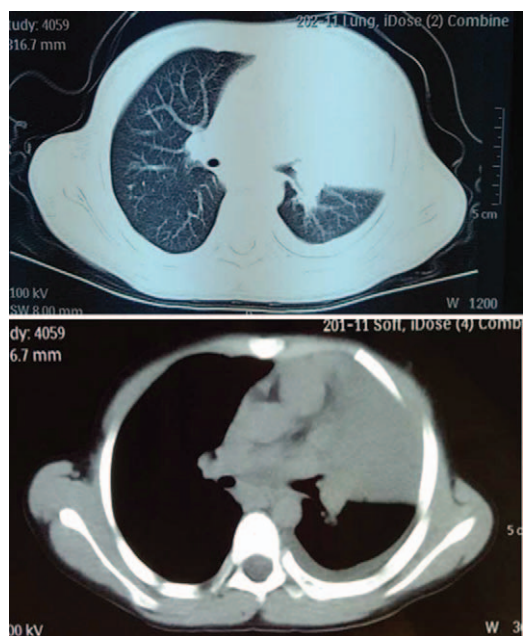


Figure 1. Chest computed tomography (CT) scan of a 7-year-old boy with *Mycoplasma pneumoniae* pneumonia complicated with cerebral infarction reveals solidification of the left lung with atelectasis of the left upper lobe and left pleural effusion.

no exudation. The lower left lung had diminished vocal fremitus and was dull on percussion, and rales were heard. Neurological examination was unremarkable. There was also no other remarkable abnormality.

Laboratory examinations, including routine blood chemistry and blood count, and C-reactive protein, revealed no abnormality. Chest CT scan revealed left lung solidification with atelectasis of the left upper lobe and left hydrothorax (Fig. 1). Serum *M pneumoniae* IgM was positive (titer 1:640). Pleural fluid was aspirated and was clear and the protein content in the pleural fluid (37,472.0mg/L) and LDH content (2340units/L) in the pleural fluid indicated exudates. The *M pneumoniae* DNA content in the pleural effusion was 1.0×10^4 copies/mL. A diagnosis of severe *M pneumoniae* pneumonia was made.

Considering the antibiotics resistance spectrum of *Streptococcus pneumoniae* in the region and according to the China Community Acquired Pneumonia (CAP) Treatment Guideline (2013), the boy was given meropenem (20mg/kg, 3 times daily) and azithromycin (10mg/kg, once daily). Fever still persisted at 48hours post-admission and the erythrocyte sedimentation rate (ESR) was 34 mm/hour (normal reference, 0–20mm/hour), C-reactive protein 138mg/L (normal reference, 0–8mg/L), and LDH 720units/L (normal reference, 120–300units/L). Methylprednisolone was given intravenously (1.5mg/kg, twice daily). Temperature was at 39.7°C. The adenosine deaminase (ADA) content in pleural effusion was 66.1 units/L on December 26, 2016 and 59.6 units/L on December 28, 2016. Given that the ADA content was above the threshold value for tuberculosis (45 units/L) and the region was endemic for tuberculosis, isoniazid and rifampin (10 mg/kg.d, once daily at bedtime) were given prophylactically. Bronchoscopy revealed massive cordlike plugs in the bronchial cavity of the anterior segment of the left upper lobe, the lingua and the posterior basal segment of the left lower lobe (Fig. 2). Pathology confirmed plastic bronchitis type 1 (Fig. 3).

At day 7 after admission, the patient showed impaired consciousness, aphasia, flattened left nasolabial fold, and left

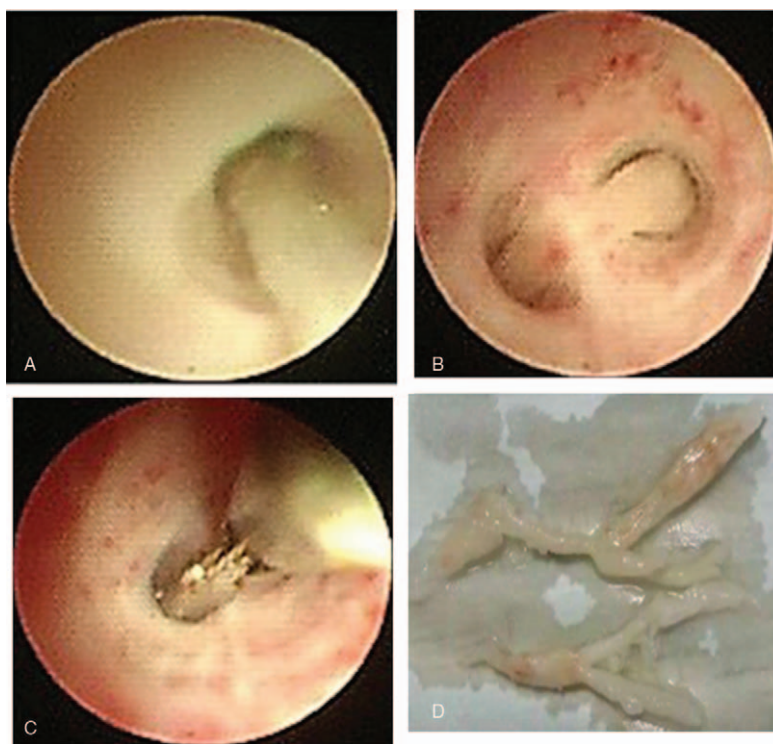


Figure 2. Bronchoscopy reveals massive cordlike plugs in the bronchial cavity of the anterior segment of the left upper lobe (A), the lingua (B), and the posterior basal segment of the left lower lobe (C). (D) Cords removed during bronchoscopy showing a branching pattern. The longer cord is 2.5cm with a diameter of 0.4 and the shorter one is 1.2cm with a diameter of 0.2.

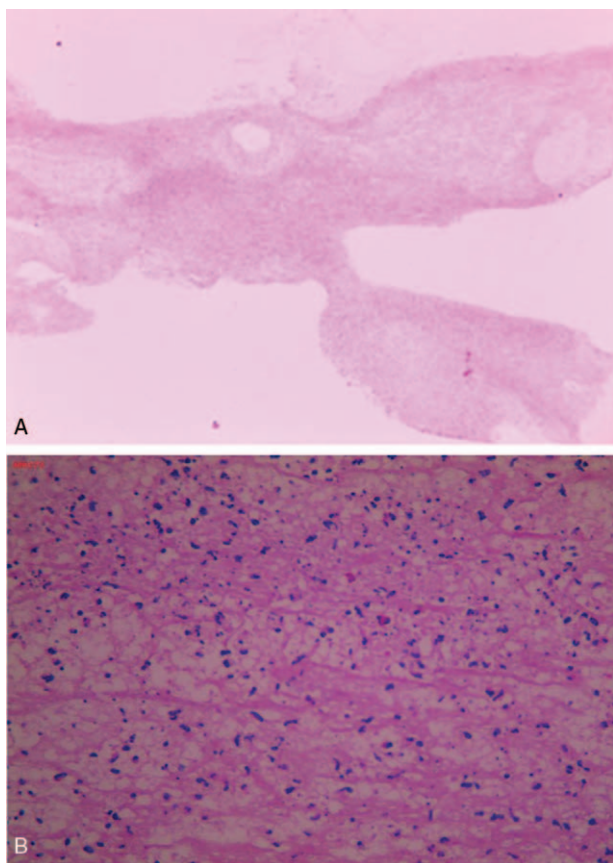


Figure 3. Pathologic examination of bronchoalveolar lavage fluid shows type 1 plastic bronchitis. Hematoxylin and eosin (H&E) staining. Magnification, 10× (A) and 40× (B).

deviation of the protruded tongue. The muscle strength of both the right upper and lower limb was grade 1, and that of both the left upper and lower limb was grade 3. Magnetic resonance angiography (MRA) failed to visualize the left internal carotid artery, the middle cerebral artery (MCA) and its distal branches (Fig. 4A). MRI DWI demonstrated hyperintensity in the left frontoinsular cortex, involving the internal capsule and basal

ganglia (Fig. 4B). Cerebral infarction was considered. Severe *M pneumoniae* pneumonia complicated with cerebral infarction was considered.

Coagulation studies revealed increased fibrin D-dimer level (10.4 mg/L; normal reference values, 0–0.3 mg/L). Enteric coated aspirin (4 mg/kg body weight, 3 times per day), low molecular weight heparin calcium (80 IU/kg body weight, once daily), and furosemide and mannitol were administered to lower intracranial pressure and low molecular weight dextran for symptomatic treatment. Methylprednisolone was adjusted to 2 mg/kg body weight, 3 times daily and tapered over 2 weeks and gamma immunoglobulin was given on December 30, 2016 at 1 g/kg body weight, once daily for 2 days. At 8 days postadmission, his body temperature returned to normal, and his consciousness was improved, but the patient still felt drowsy. At 2 weeks postadmission, his fibrin D-dimer level decreased to 1.0 mg/L and the boy spoke, though indistinctly, and had longer wake time. At 1 month, the boy walked with assistance, but still uttered indistinctly. His left upper and lower limb muscle power was normal and the right upper and lower limb muscle power was grade 3. He was discharged from the hospital and prescribed with aspirin (75 mg, once daily). The patient was followed up for 6 months. At the 6-month follow-up visit, the muscle power of bilateral upper and lower limbs was normal except still poor right handgrip power. MRA indicates improved collateral circulation in the patient. Blood chemistries and platelet counts were normal, and aspirin was discontinued.

3. Discussion

M pneumoniae pneumonia is a common cause of community acquired pneumonia in children, with a seroprevalence rate of 10 to 30%.^[8] Most infections by *M pneumoniae* are asymptomatic and self-limited, but may exhibit a myriad of symptoms and signs. In rare and severe cases, *M pneumoniae* infection may extend beyond the lungs, with the central nervous system a common site of extrapulmonary manifestations of *M pneumoniae* infection, which are seen in 1.0% to 4.8% of *M pneumoniae* infections.^[9,10] Cerebral infarction is a rare extrapulmonary manifestation of *M pneumoniae* infection and only anecdotal cases have been reported. Using the census data in Hong Kong, Chung and Wong identified 94 children with stroke among children <15 years of age in Hong Kong from 1998 to 2001, and *M pneumoniae* infection was not reported to be a cause of pediatric stroke in the patients.^[6] In a clinical series of 65

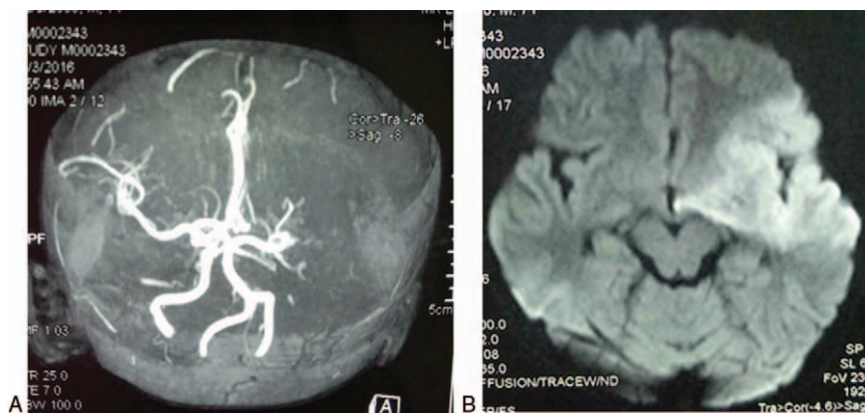


Figure 4. MRA fails to visualize the left internal carotid artery, the MCA, and its distal branches, suggesting the presence of cerebral infarction (A). MRI DWI demonstrates hyperintensity in the left frontoinsular cortex, involving the internal capsule and basal ganglia (B). MCA=middle cerebral artery, MRA=magnetic resonance angiography.

Table 1
Summary of reported pediatric cases of *M pneumoniae* pneumonia complicated with stroke or cerebral infarction.

| References | Case no | Age, y | Sex | <i>M pneumoniae</i> IgM antibody titers | Main stroke symptoms | Culprit vessels | Main treatment | Outcome |
|-------------------------------|---------|--------|------|--|--|--|---|--|
| Tirado et al ^[19] | 1 | 6 | Boy | | Cortical blindness | PCA occlusion | Acetylsalicylic acid (5 mg/kg/d), heparin (1 mg/kg/d), azithromycin (1500 mg/3 d), and prednisolone (80–20 mg/). | Visual acuity was completely recovered, but visual field testing revealed a right hemianopsia which persists |
| Garcia et al ^[20] | 2 | 13 | Girl | 1.5 units/L (normal <0.76) | Mild left sided weakness and ataxia | Right ACA/MCA and left MCA | Broad-spectrum antibiotics; extracorporeal membrane oxygenation | Patient expired; diffuse ischemic infarcts on autopsy |
| Kong et al ^[21] | 3 | 11 | Girl | 1:320 | Hemiplegia and aphasia | Occlusion of bilateral MCA, mainly on the left side | Azithromycin, hormone and heparin, and rehabilitation training | Recovery at 10 mo |
| Fu et al ^[13] | 4 | 5 | Girl | 1:1024 | Expressive aphasia, dense hemiplegia, and upgoing plantar reflex on the right side | Occlusion of left MCA | Erythromycin and rehabilitation training | Recovery at 4 mo with hemiplegic gait |
| Pariker et al ^[22] | 5 | 8 | Girl | 1: 16,384 (highest) | Facial weakness, hemiparesis, dysphagia, and dysarthria | Slow filling of penetrating branches of left MCA | Ampicillin and gentamicin | Recovery at 8 wk |
| Kang et al ^[14] | 6 | 5 | Girl | 5021 U/mL for IgM (normal range, 0–949 U/mL) | Left hemiparesis and left facial palsy | Complete occlusion of the right MCA at the M1 portion | Ceftriaxone and clarithromycin for 14 d, mannitol for 7 d, intravenous methylprednisolone for 3 d, aspirin at doses of 2 mg/kg given daily, and rehabilitation therapy | Partial improvement; discharged from hospital at day 32 |
| Gu et al ^[15] | 7 | 8 | Boy | 1:640 | Hemiparesis, brain hernia | Occlusion of right MCA | Broad-spectrum antibiotics; azithromycin; methylprednisolone | Death |
| | 8 | 5 | Boy | 1:640 | Frequent convulsions, coma | Occlusion of the basilar artery and PCA | Broad-spectrum antibiotics; azithromycin; methylprednisolone; hyperbaric oxygen | Poor recovery of brain function; the patient died 3 mo posthyperbaric oxygen therapy |
| The current case | | 7 | Boy | 1:640 | Reduced consciousness, aphasia, flattened left nasolabial fold, and left deviation of the protruded tongue; reduced muscle power | Occlusion of the left ICA, the MCA and its distal branches | Meropenem (20 mg/kg, 3 times daily) and azithromycin (10 mg/kg, once daily); methylprednisolone was given intravenously (2 mg/kg, thrice daily) and gamma immunoglobulin (1 g/kg body weight, once daily for 2 d); aspirin and low molecular weight heparin | Recover at 6 mo with poor right handgrip power |

ICA = internal carotid artery, MCA = middle cerebral artery, PCA = posterior cerebral artery.

pediatric cases of ischemic stroke from China, only 1 child had *M pneumoniae* infection-associated ischemic stroke.^[7] The current case initially showed manifestations of *M pneumoniae* pneumonia and despite aggressive antibiotic therapy and antiinflammatory therapy, the patient failed to respond. The onset of neurologic symptoms and MRA findings strongly indicated the development of cerebral infarction in the patient.

The mechanisms underlying *M pneumoniae* infection-associated cerebral infarction remain unelucidated. It has been speculated that *M pneumoniae* may disrupt the integrity of the vascular endothelium and upset the equilibrium between coagulation and anticoagulation by eliciting an inflammatory response, which may lead to hypercoagulation and thrombosis.^[11] Direct invasion by *M pneumoniae*, neurotoxin production, immune-mediated mechanisms, and cytokine production have also been implicated.^[12] Our patient had normal coagulation, but showed elevated fibrin D-dimer levels, suggesting a hypercoagulable state. Elevated fibrinogen and fibrin D-dimer levels were also reported in an 11-year old girl^[13] and a 5-year old girl^[14] with *M pneumoniae* pneumonia complicated with occlusion of the MCA (Table 1). Gu et al^[15] reported a series of 6 pediatric cases of *M pneumoniae* pneumonia, including one case complicated with occlusion of the right MCA and cerebral infarction and one case with occlusion of the basilar artery and posterior cerebral artery and brain infarction. Four of these patients had elevated D-dimer levels. Anticoagulation therapy with aspirin for 6 months and low molecular weight heparin calcium reduced fibrin D-dimer levels to 1.0 mg/L at day 4 postinfarction. Thrombolytic therapy is considered the optimal modality for acute ischemic stroke in adults; however, the optimal approach for managing pediatric stroke remains elusive. Gu et al treated 2 children with cerebral infarction with thrombolytic therapy; one died of brain herniation while the other lost consciousness.^[15] The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines for Antithrombotic Therapy and Prevention of Thrombosis does not recommend thrombolytic therapy for unimportant minor brain infarcts.^[16] In our current case, no thrombolytic therapy was performed given the presence of severe pneumonia and poor tolerance of anesthesia and aspirin and lower molecular weight heparin were given instead.

We reviewed 20 pediatric cases of *M pneumoniae* pneumonia complicated with stroke or cerebral infarction. The MCA was involved in 13 (65.0%, 13/20) patients, the posterior cerebral artery (PCA) in 4 (20%, 4/20) patients, and the internal carotid artery (ICA) in 5 patients (25%, 5/20) (the ICA and MCA were involved in 2 patients). The predominance of MCA involvement is consistent with previous reports.^[17,18] Anatomically, the M1 segment of the MCA begins at the terminal bifurcation of the ICA and ends at the genu, a right-angle bend in the artery as it courses over a small gyrus of the insular cortex, where it is predisposed to thrombosis or occlusion. The early signs of pediatric stroke or cerebral infarction may be subtle and escape notice and only when altered consciousness, hemiplegia, or other neurologic symptoms emerge, involvement of the central nervous system is suspected. MRI DWI, as performed in the current case, can detect brain lesions within 6 hours of onset of stroke and is capable of distinguishing new versus old infarct.

Treatment of *M pneumoniae* pneumonia complicated with stroke or cerebral infarction requires aggressive antibiotic therapy, anticoagulation therapy as well as antiinflammatory therapy. Symptomatic management like controlling elevated intracranial pressure and rehabilitation training is also important to recovery.

In conclusion, *M pneumoniae* pneumonia complicated with cerebral infarction in children is clinically rare, and early diagnosis and prompt treatment with multiple modalities are critical to a successful outcome.

Author contribution

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Writing – review & editing: Jie Liu.

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