Severe *Mycoplasma pneumoniae* infection in a young child: An emerging increase in incidence?

To the editor: *Mycoplasma pneumoniae* is one of the leading causes of community-acquired pneumonia in school-aged children and young adults. Although it is self-limiting, *M. pneumoniae* pneumonia (MPP) can lead to serious complications, with 25% of patients experiencing prolonged fever, worsening symptoms and deteriorating radiological findings despite appropriate macrolide therapy for ≥7 days.[1]

Macrolide resistance of *M. pneumoniae* (MRMP) is a potential cause of refractory MPP (RMPP). Differences in clinical features and severity between MRMP and macrolide-sensitive *M. pneumoniae* infections are unclear, but studies show longer fever duration, a more severe clinical course and an increased risk of intensive care unit (ICU) admission in MRMP.[2] Recent childhood pneumonia outbreaks in northern China may be due to post-pandemic changes in endemic respiratory infections, similar to US and European outbreaks in 2022. Epidemiological evidence suggests that re-emerging infections by organisms such as respiratory syncytial virus, influenza viruses and *M. pneumoniae* are the cause.[3] Non-pharmaceutical interventions significantly reduced *M. pneumoniae* transmission during the COVID-19 pandemic to 1.69% between 2020 and 2021, compared with a global incidence of 8.61% between 2017 and 2020. A resurgence of *M. pneumoniae* in an unexposed population during the pandemic may result in an increase in severe disease.

We present the case of a young child with severe MPP (SMPP) who required paediatric ICU care and did not respond to azithromycin. The parents gave consent for the publication of the case report.

A 5-year-old HIV-negative boy presented with a history of fever, persistent cough and tachypnoea for 8 days. He had completed a course of oral amoxicillin/clavulanate with no improvement. He had previously been well, with no contact with tuberculosis or significant travel history. On examination, he had a fever and reduced air entry in the right lower lobe (RLL) area. A chest radiograph (CXR) confirmed RLL airspace disease and obscuration of the right hemidiaphragm (Fig. 1A). Because the fever persisted, the CXR was repeated after 3 days, confirming worsening consolidation and a small pleural effusion (Fig. 1B). *M. pneumoniae* was confirmed on nasopharyngeal aspirate by polymerase chain reaction (PCR) on day 8. No other viruses or bacteria were identified. The C-reactive protein (CRP) level remained low (Table 1), but persistent swinging fever of 40˚C was present. On day 5 of treatment with intravenous cefuroxime and oral azithromycin, the boy developed respiratory distress requiring escalation to high-flow nasal cannula respiratory support. The follow-up CXR demonstrated an expansile RLL pneumonia, significant effusion with mediastinal shift to the left, and parenchymal disease in the left lower lobe (Fig. 1C).

An ultrasound scan confirmed a large uncomplicated effusion with underlying RLL consolidation (Fig. 1D). Pleural fluid was drained, yielding 800 mL. A post-contrast computed tomography (CT) scan also showed parenchymal airspace consolidation of the RLL with a bulging anterior margin, as well as left-sided airspace consolidation and a left-sided effusion (Fig. 1E - H).

On day 8, the CXR showed improvement in the effusion size, but there was residual parenchymal airspace disease in the RLL (Fig. 1I). PCR testing for *M. pneumoniae* was positive in the pleural fluid on the Biofire FilmArray Pneumonia Panel (BioFire PN; BioMérieux, France) (Table 1). In view of the persistent symptoms, radiological features of severe disease and no response to azithromycin, the therapy was changed to doxycycline to treat presumptive resistant mycoplasma. Oral prednisone was added owing to prolonged symptoms and high ferritin levels (213 µg/L). The fever improved after 48 hours. The pigtail catheter was removed after 5 days.

The treating clinicians were informed that there were three other microbiologically confirmed MPP cases at the patient's school, two children of the same age and an adult. They were all effectively treated at home with azithromycin.

A CXR on day 15 and after completion of 10 days of doxycycline demonstrated marked improvement of both the effusion and the parenchymal airspace disease (Fig. 1J).

MPP in South African children may be on the rise, but lack of access to serological and molecular testing in the public sector may mean that there is a paucity of data.

MPP, or 'walking pneumonia', is a benign, self-limiting disease characterised by subacute fever, cough, asthma-like symptoms and dyspnoea. Some children cannot be effectively treated with 7 days of macrolides, leading to RMPP.[4] RMPP is defined as no significant improvement, worsening lung disease or complications. Patients have longer fever duration, longer hospitalisation, and a higher incidence of extrapulmonary complications. Radiological findings include lobar consolidation, lobar atelectasis, pleural effusions and bronchopneumonia.[5]

Expansile pneumonia, as was seen in the case reported here, is not a common presentation. CT scans have shown that the incidence of lung consolidation and pleural effusion was higher in MRMP than in non-resistant MPP.[6]

Serum ferritin levels have been reported as an indicator of the severity of MPP and have been used in making the decision whether to add corticosteroid therapy.[7]

D-dimer results predict severe disease, SMPP with D-dimer levels >0.308 mg/L being associated with more complications such as pleural effusion and myocardial and liver damage. In our case, the D-dimer level was 3.41 mg/L.[8]

SMPP patients have a higher prevalence of sputum plugs than patients with non-severe MPP. These plugs are caused by bronchial inflammation and ciliary abnormalities, which can result in increased mucus production and decreased mucus clearance, leading to sputum plug formation.

MPP patients requiring ICU care have higher white blood cell counts, CRP levels and alanine transaminase than those who are less severely ill, and are more likely to have underlying illnesses and pleural effusion.[9] Studies indicate that 71 - 88% of macrolide-sensitive MPP patients are free of fever within 48 hours of starting treatment. In macrolide-resistant MPP patients, fever remains in 52 - 73% and

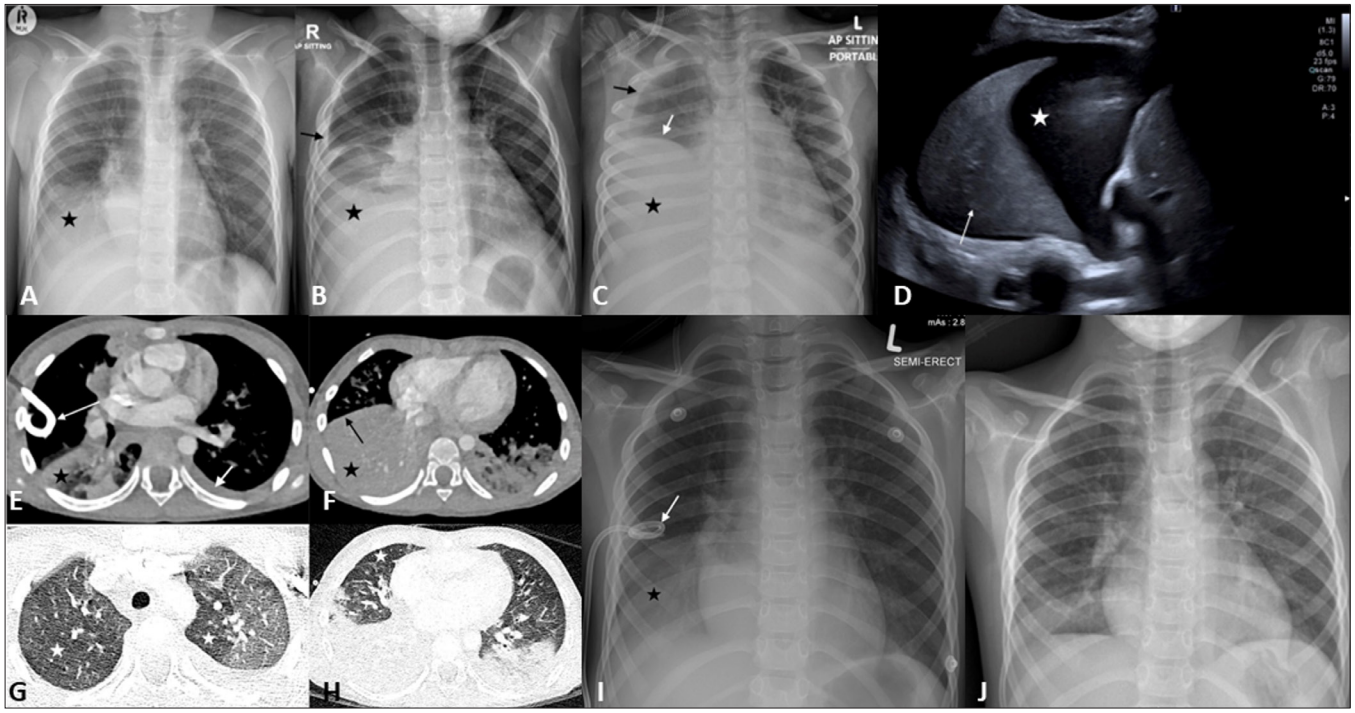

Fig 1. (A) Day 1. Frontal plain CXR demonstrating airspace disease in the RLL (star) resulting in obscuration of the right hemidiaphragm. (B) Day 3. Frontal plain CXR demonstrating progression of the RLL airspace disease (star) and development of a lamellar effusion (black arrow) tracking also into the minor fissure. (C) Day 5. Frontal plain CXR demonstrating further expansion of the RLL airspace process (star) with a convex superior border (white arrow), in keeping with an expansile pneumonia, and enlargement of the right effusion (black arrow), now tracking over the apex of the lung. There is also some loss of clarity of the left hemidiaphragm in keeping with developing parenchymal disease in the left lower lobe. (D) Ultrasound scan after day 5. Longitudinal ultrasound scan of the right chest demonstrating a large simple effusion (star) and the underlying consolidated lung (arrow). (E and F) Post ICD CT scan demonstrating sequential images of a post-contrast scan of the chest on soft-tissue windows, confirming the appropriate intrathoracic location of the thoracic drain (long white arrow in E) and parenchymal airspace consolidation of the RLL (stars in E and F), with normal vascular enhancement but showing a bulging anterior margin (black arrow in F), as well as left-sided airspace consolidation and a left-sided effusion (short white arrow in E). (G and H) Axial sequential images of the same CT scan on lung windows, demonstrating areas of localised air trapping (white stars) in addition to the multifocal airspace disease. (I) Day 8 post ICD. Frontal CXR demonstrating a right thoracic pigtail drain in situ (arrow), with marked improvement in the size of the effusion but with residual parenchymal airspace disease in the RLL (star). (J) Day 15. Frontal CXR demonstrating marked improvement of both the effusion and the parenchymal airspace disease, with only a small residual area of parenchymal density on the RLL and reappearance of the hemidiaphragms bilaterally. (CXR = chest radiograph; RLL = right lower lobe; ICD = intercostal chest drain; CT = computed tomography.)

30% for more than 48 and 72 hours, respectively. Tetracyclines and fluoroquinolones can be considered for patients who do not respond to macrolides, but the minimum inhibitory concentrations of azithromycin often exceed 64 mg/mL.[10]

Okada *et al*.[11] reported that fever subsides within 72 hours of switching to tetracyclines (doxycycline or minocycline) or fluoroquinolones in nearly all patients with macrolide-resistant MPP.

Doxycycline and other tetracyclines are contraindicated in children aged <8 years owing to permanent tooth discoloration and enamel degradation. Studies show that doxycycline is less likely to cause enamel staining because it binds to calcium less readily. The American Academy of Pediatrics now recommends use of doxycycline for short periods.[12,13]

When combined with macrolide treatment in SMPP, prednisolone significantly reduces fever, dyspnoea and hypoxaemia, accelerates radiological improvement, and reduces serum ferritin and lactate dehydrogenase levels.[14]

The incidence of MPP has been increasing globally during the post-COVID-19 pandemic period.[15] The reasons for the increase are unknown, but may be related to the fact that large sectors of the population were not exposed during the pandemic. Our case demonstrates that MPP can present as severe disease needing ICU admission, as well as the possibility that patients with RMPP may require doxycycline and corticosteroids.

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Table 1. Laboratory results

	Patient's result	Reference range
Complete blood count		
WBC count (× 109/L)	10.8	6 - 16
Neutrophils (× 109/L)	7.34	2.4 - 7.50
Lymphocytes (× 109/L)	1.37	2.3 - 8.0
MCV (fL)	89.5	75 - 87
MCH (pg)	114	24 - 30
MCHC (g/dL)	127	31 -3 7
Serum biomarkers		
Serum ferritin (µg/L)	213	4 - 67
CRP (mg/L)	6	<10
LDH (U/L)	688	110 - 295
D-dimers (mg/L)	3.41	0.00 - 0.25
Bilirubin (µmol/ L)	6	5-21
Troponin (ng/L)	<3	Abnormal >100
Pleural aspirate analysis		
Pleural fluid protein (g/dL)	37	<1.5
Pleural fluid LDH (U/L)	1 406	n/a
Pleural fluid ADA (U/L)	24.7	4.8 - 38
Pleural fluid cell counts		
Neutrophils (%)	7	0 - 2
Lymphocytes (%)	89	2 - 11
PCR tests		
SARS-CoV-2 antigen	Negative	n/a
Xpert MTB/RIF	Negative	n/a
Mycoplasma pneumoniae PCR	Positive	n/a
Viral PCR	Negative	n/a
Bacterial PCR	Negative	n/a
Malignant cytology	Negative	n/a

WBC = white blood cell; MCV = mean corpuscular volume; MCH = mean corpuscular haemoglobin; MCHC = mean corpuscular haemoglobin concentration ; CRP = C-reactive protein; LDH = lactate dehydrogenase; n/a = not applicable; ADA = adenosine deaminase; PCR = polymerase chain reaction.

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