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Case Report

Refractory *Mycoplasma pneumoniae* with cytokine storm: a case report with an atypical presentation

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ABSTRACT

Mycoplasma pneumoniae is a significant cause of community-acquired pneumonia in children. Macrolide-resistant M. pneumoniae (MRMP) has been observed worldwide, with varying incidence rates. MRMP infections have a poor response to macrolide antibiotics, which further results in prolonged fever, extended antibiotic treatment, increased hospitalization, critical care unit admissions, and a significantly higher proportion of patients needing to receive glucocorticoids or second-line antibiotics. A 5-year-old girl presented with high-grade fever and lobar consolidation due to *M. pneumoniae*. She didn't respond to macrolides. She developed features of cytokine storm with elevated ferritin, transaminitis etc. She was started on levofloxacin, given intravenous immunoglobulin and systemic corticosteroids, following which defervescence occurred. Early and rapid identification of resistant Mycoplasma infection is important. Appropriate antibiotic treatment, along with immunosuppressive therapy, is warranted for children with refractory *M. pneumoniae pneumonia* (MRMP).

Keywords: Refractory mycoplasma, Cytokine storm, *M. pneumoniae*

INTRODUCTION

Mycoplasma pneumoniae is an important cause of respiratory infections in children, contributing to 20-40% of community-acquired pneumonia in children. The incidence is higher in older children and during epidemics. Usually, *M. pneumoniae* infections are self-limiting. The majority of mycoplasma infections are mild with a good prognosis. Macrolides are the preferred antibiotics for *M. pneumoniae* infections in children. Infections with MRMP have become more prevalent globally. In the eastern parts of Asia, the isolation rate of MRMP has reached as high as 70-90%, posing huge challenges for pediatricians.[1]

In the absence of effective antibiotics, severe MRMP infections result in prolonged hospitalization due to unresolved fever and complications. Still, there remains a lack of global consensus on the diagnosis and treatment of MRMP in children.

We report a 5-year-old girl presenting with high-grade fever, lobar consolidation diagnosed with *M. pneumoniae*, not responding to macrolides, subsequently developing features of cytokine storm, and finally responding to intravenous immunoglobulins (IVIG) and glucocorticoids.

CASE REPORT

Five-year-old girl presented with high-grade fever preceded by upper respiratory tract symptoms. Upon examination, the child was febrile with no respiratory distress, maintaining saturation in room air, and hemodynamically stable. On auscultation, bronchial breathing was heard in the right infraclavicular area. X-ray chest showed features suggestive of right lobar consolidation (Figure 1).

The pneumonia panel was positive for *M. pneumoniae*. Laboratory investigations showed normal WBC, mildly

elevated CRP, and procalcitonin. The child was started on amoxillin-clavulinic acid and azithromycin. Fever spikes persisted despite starting on antibiotics, and was admitted.

Management and outcome

Laboratory parameters and X-ray were repeated, and started on IV ceftriaxone and clindamycin. On the 5th day after starting antibiotics, high-grade fever spikes persisted, with the child developing features of capillary leak in the form of eyelid edema, hepatomegaly. Repeat labs showed hyponatremia, transaminitis, elevated ferritin and LDH, though CRP and procalcitonin were only mildly elevated. ECHO cardiogram was normal. USG showed mild hepatomegaly. Antibiotics were upgraded to piperacillin-tazobactam for broader coverage and levofloxacin to cover resistant *Mycoplasma*. Since fever spikes persisted with features of cytokine storm, the child was started on IVIG. 2 g/kg of IVIG was given and since fever spikes were persistent, the child was given low dose glucocorticoids. Fever spikes drastically reduced, and inflammatory markers started coming down and the child was discharged home.

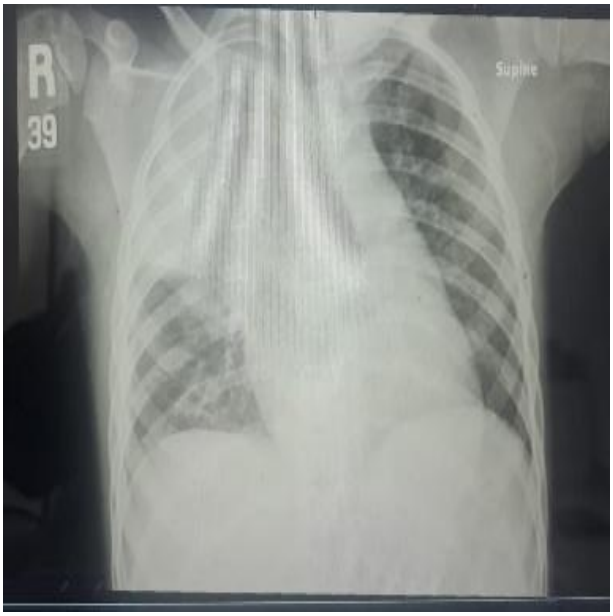

Figure 1: Chest X-ray.

DISCUSSION

In children respiratory tract infections is an important cause of hospitalizations. Among the organisms, *M. pneumoniae* accounts for 20-40% of total cases of community-acquired pneumonia in children, and nearly 20% of cases requires hospitalization.[2] Usually, school going children are commonly affected, hence the name walking pneumonia. Mostly, *Mycoplasma* infections are self-limiting, but in some children, they can cause prolonged fever and complications. MRMP has been observed worldwide and can complicate treatment as ineffective antibiotics can lead to pneumonia progression or more extrapulmonary complications.[3] It has been observed that children with MRMP infections have persistent fever, increased oxygen requirements, need for intensive care unit admission, prolonged course of multiple antibiotics, and subsequently all these result in prolonged hospital stay.[2] As such the admission to the pediatric intensive care unit was also found to be increased in children with MRMP infection. MRMP pneumonia often has outbreaks leading to transmission within schools, close contacts, and within households, causing significant socioeconomic burdens.[2,3] The severity of mycoplasma infection usually correlates with the intensity of the host immune response. Hence when there is a hyperimmune response, immunosuppressive therapy, along with appropriate antibiotic treatment, is beneficial for children with refractory *M. pneumoniae* pneumonia.[4]

M. pneumoniae strains having a minimum inhibitory concentration (MIC) of 1 mg/l are considered resistant. Currently, most isolates of MRMP from patients have MIC values of ≥128 and ≥2 mg/l for erythromycin and azithromycin, respectively. M. pneumoniae strains are considered sensitive to doxycycline when the MIC values are ≤2 mg/l, and to minocycline ≤4 mg/l. Currently, MRMP organisms are sensitive to both doxycycline and minocycline. Among quinolones, levofloxacin is considered sensitive when MIC value is ≤1 mg/l, and for moxifloxacin ≤0.5 mg/l. Currently, MRMP isolates are sensitive to all quinolone antibiotics, such as levofloxacin and moxifloxacin.[5]

Clinical symptoms, laboratory findings, and imaging manifestations of MRMP are similar to those of MSMP. However, MRMP pneumonia are characterized with prolonged fever, requiring longer duration of antibiotics, higher rates of antibiotic change, and increased use of corticosteroids compared to MSMP pneumonia.[6] Serum lactate dehydrogenase (LDH), D-dimer, and other inflammatory markers can be used to predict MRMP pneumonia; however, there is no single diagnostic tool to determine *M. pneumoniae* resistance. Clinical symptoms, laboratory markers, chest imaging findings, and bronchoscopy findings can be similar in both macrolide-sensitive and resistant *Mycoplasma* infection, except that clinical symptoms persist in resistant mycoplasma. LDH and ferritin levels correlate with the severity of the inflammatory response in Mycoplasma pneumonia and may serve as biomarkers to determine the requirement of glucocorticoids.[7] Ideally, polymerase chain reaction (PCR) and fluorescent probe technology are used for the rapid diagnosis of MRMP by detecting point mutations associated with macrolide resistance in *M. pneumoniae*. Also, *in vitro* cultivation of *M. pneumoniae* and drug susceptibility testing can be used to analyze the resistance of *M. pneumoniae* to antimicrobial drugs.[7] But these tests are not available easily, and MRMP pneumonia is diagnosed based on persistence of symptoms and

elevated biomarkers like LDH and ferritin when there is a hyperimmune inflammatory response.

Currently, there is no consensus for treating MRMP pneumonia. Various guidelines recommend tetracyclines and fluoroquinolones as second-line treatment options for *M. pneumoniae* infections. Guidelines from Japan and Taiwan indicate that if fever persists or chest imaging continues to worsen after 48-72 hours of macrolide treatment, then second-line agents such as fluoroquinolones or tetracyclines should be considered.[8] Routine systemic glucocorticoids are not recommended for MRMP pneumonia. Only for severe or critical MRMP pneumonia, systemic glucocorticoid therapy should be considered. These include those patients who develop extrapulmonary complications, increased oxygen requirement, or in those with cytokine storm features. Also, it is necessary to rule out immunocompromised states or coinfection with other organisms before initiating steroids. Recommended initial dose of methylprednisolone is 1-2 mg/kg/day. If there is no improvement after 24 hours of initial treatment, it can be increased to 4-6 mg/kg/day. Once the clinical symptoms improve, and inflammatory markers decrease, glucocorticoids should be gradually tapered off, usually over a course of 3-5 days.[9] IVIG is not routinely recommended to use in the treatment of MRMP pneumonia. However, IVIG therapy may be considered when severe extrapulmonary complications such as central nervous system damage, cutaneous lesions, hematological manifestations, or other severe extrapulmonary complications occur. It is suggested to administer IVIG at 1 g/kg/day once daily for 1-2 days.[10] In this case, the child didn't improve after azithromycin. Subsequently, levofloxacin was started, but she still developed features of cytokine storm. The respiratory panel was positive only for mycoplasma pneumoniae. Finally, she improved drastically after starting steroids. Though usually *Mycoplasma* infections present with fever, wheezing, and non-specific respiratory symptoms, it is known to present with lobar consolidation similar to this case and can also present with pleural effusion. During follow up, the right upper lobe consolidation completely resolved, and the child was doing well.

CONCLUSION

MRMP pneumonia has become more prevalent worldwide in recent years, resulting in a greater disease burden. In those patients who don't respond within 48-72 hours after starting macrolides or deteriorate rapidly despite macrolides, MRMP should be considered, and second-line agents should be used. Early and rapid identification of MRMP is now available by PCR and fluorescent probe techniques in respiratory specimens and should be used wherever available. Although the rate of resistance to macrolide remains high, *M. pneumoniae* still has good *in vitro* sensitivity to second-line agents such as tetracyclines and quinolones, hence should be used judiciously in those patients requiring. Though tetracycline and quinolone have been associated with side effects in children, it is well tolerated and safely used for a shorter course. Additionally, it is necessary to develop an antibiotic stewardship program to reduce the prevalence of MRMP strains. For severe or critical MRMP pneumonia, systemic glucocorticoids should be considered. Immunosuppressive therapy, along with appropriate antibiotic treatment, is needed for children with refractory *M. pneumoniae* pneumonia (MRMP).

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