

CASE REPORT

DUAL INFECTION : DENGUE HEMORRHAGIC FEVER WITH UNUSUAL MANIFESTATIONS AND MYCOPLASMA PNEUMONIA IN A CHILD

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Abstract. We report a case of pneumonia caused by *Mycoplasma pneumoniae* in an 8-year-old Thai girl. She had a dual infection with dengue hemorrhagic fever with unusual manifestations; liver failure. The diagnoses were based on relevant clinical findings and laboratory confirmations of both infections.

M. pneumoniae is a common cause of respiratory tract infection. Clinical manifestations include pharyngitis, bullous myringitis, tracheo-bronchitis or pneumonitis. It can involve various other organs (Murray, 1988). Clinical manifestations of mycoplasma pneumonia may overlap with other viruses. Before concluding that the development of concurrent but perhaps unrelated events, as if they were parts of the same mycoplasma infection, one should also search for dual infections. We report an uncommon condition in a child who presented with mycoplasma pneumonia and dengue hemorrhagic fever with unusual manifestation, and discuss a possible pathogenesis and management.

An 8-year-old girl from Bangkok presented at a private hospital with a 3-week history of cough and fever. Physical examination showed bilateral inflamed tympanic membranes and crepitations over both lungs. Laboratory studies revealed hematocrit 35%, white blood cell count 9,500/mm³ with 83% neutrophils, 7% lymphocytes, platelet count 395,000/mm³. Her chest roentgenogram showed pulmonary infiltration of both lower lungs, more on the left side. Mycoplasma titer by particle agglutination was posi-

tive 1:2,560. (Commercial Science. Serodia). She was treated with clarithromycin as an outpatient. The child was admitted 3 days later with vomiting. The fever subsided with slight improvement of cough. On admission, she appeared mildly drowsy with a temperature of 37°C, pulse rate 130 beats/minute, respiratory rate 30 breaths/minute, blood pressure 90/60 mmHg and a tourniquet test was negative. Physical examination was notable for crepitation over both lungs. Her hematocrit was 51.3%, white blood cell count 22,900/mm³, with 63% neutrophil, 37% lymphocytes, platelets 31,000/mm³. Her serum sodium was 124 mEq/l, potassium 6.3 mEq/l, chloride 91 mEq/l; bicarbonate 8 mEq/l, blood urea nitrogen 60 mg/dl, and creatinine 2.9 mg/dl. Her chest roentgenogram revealed unchanged bilateral pulmonary infiltrations (Fig 1).

She received intravenous fluid and ceftriaxone. On the following day, she was dyspneic, moderately drowsy and developed tonic seizures 3 hours before she was referred to us for evaluation. Her physical examination on admission revealed a dyspneic child with hepatomegaly and drowsiness with Glasgow Coma scale of 9 (2 eyes opening, 2 verbal, 5 motor), hyperreflexia, no meningeal signs but positive clonus sign. Heart rate was 158 beats/minute, respiratory rate 50 breaths/minute, blood pressure 100/70 mmHg, temperature 36.3°C. Laboratory data

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included white blood cell count of $28,400/\text{mm}^3$ with 90% neutrophils, 2% lymphocytes, 6% atypical lymphocytes, 1% monocytes, and 1% eosinophils. Hematocrit was 46.3% and platelet count $16,000/\text{mm}^3$. A chemistry panel showed sodium 129 mEq/l, potassium 4.5 mEq/l, chloride 94 mEq/l, bicarbonate 17 mEq/l, blood urea nitrogen 51 mg/dl, and blood creatinine 2.4 mg/dl. Blood glucose 118 mg/dl, alanine aminotransferase 1532 U/l, aspartate aminotransferase 5,466 U/l, partial thromboplastin time and prothrombin time were 64.4 seconds prolonged (control 28.4 seconds) and 27.7 seconds (control 11.5 seconds) respectively. Liver function test on the following day showed total bilirubin 1.07 mg/dl, direct bilirubin 0.5 mg/dl, alkaline phosphatase 84 U/l, alanine aminotransferase 2,683 U/l, aspartate aminotransferase 19,720 U/l, albumin 2.4 mg/dl, globulin 1.9 mg/dl, ammonia 118 $\mu\text{g}/\text{dl}$, γ -glutamyl transpeptidase 53 U/l, and elevated fibrin degradation product $> 20 \mu\text{g}/\text{ml}$. Her chest roentgenogram revealed unchanged infiltrations and bilateral pleural effusion (Fig 2). Cranial computerized tomography showed diffuse swelling of the brain. She was intubated and hyperventilated to reduce brain edema. Intravenous fluid was initiated to replace the leakage. That evening, she developed a fever of 39°C which lasted for another 4 days. Cefotaxime was given and clarithromycin was discontinued because of concern over drug-induced hepatitis. She developed evidence of excessive capillary permeability which manifested as generalized edema, ascites, and increased bilateral pleural effusions. She developed epistaxis, upper gastrointestinal bleeding and blood oozing from her venesection wound. Her hematocrit dropped to 24%. Then, she received multiple packs of red cells, and fresh frozen plasma and platelet transfusions. Her hematocrit and platelet count were stabilized after 4 days of hospitalization and normalized by the 13th hospital day. During the first 48 hours of hospitalization, she developed oliguria with urine output of 0.5 ml/kg/hr and received multiple doses of furosemide and dobutamine intravenously. Her blood urea nitrogen and creatinine rose to 80 mg/dl and 5.4 mg/dl, respectively by the 13th day in hospital. She developed hypertension with blood pressure of 130/93 and was treated with oral anti-



Fig 1—Chest radiograph showing pulmonary infiltration both lower lungs.



Fig 2—Chest radiograph showing unchanged infiltration and bilateral pleural effusion.

hypertensive drugs. Ultrasonography of her kidneys revealed an acute or subacute process of renal parenchymal disease compatible with acute tubular necrosis. A diagnosis of dual infections with dengue virus and mycoplasma was made. Additional laboratory studies revealed dengue IgM by rapid test, positive dengue virus RNA type 3 detected by RT-PCR, dengue titer by hemagglutination inhibition test for dengue type 2 of 1:160, and dengue type 3 of 1:80 which rose more than fourfold to 1:2560 for both types 5 days later. The hepatitis markers for HBsAg, Anti HBc-IgM, AntiHCV AntiHAV – IgM (Abbott Laboratories, North Chicago, ILL), were all negative. The mycoplasma antibody titer by particle agglutination was > 1:81120. (Fujirebio Serodia Micro II). She received a 3-day-course of azithromycin starting on hospital day 9.

The patient's condition gradually improved and she was discharged by day 19. At follow-up, her liver and renal function tests were normal.

Pneumonia is the most commonly recognized clinical syndrome occurring with *M. pneumoniae* infections. Abnormalities in almost every organ system have been described as the extrapulmonary manifestations of *M. pneumoniae* infection (Murray, 1988). Central nervous system involvements include meningoencephalitis, transverse myelitis, aseptic meningitis, cerebellar ataxia and Guillain-Barre syndrome. Two-thirds of patients with encephalitis associated with *M. pneumoniae* infection manifest with seizures and impaired consciousness (Koskiniemi *et al*, 1993). Common hematological manifestations include hemolytic anemia (Tanowitz *et al*, 1978). Thrombocytopenia and coagulation defect with *M. pneumoniae* infection are rare. Disseminated intravascular coagulation (DIC) is observed in cases of severe infection (Chryssanthopoulos *et al*, 2001). Hepatitis associated with *M. pneumoniae* infection is usually mild and renal involvement is uncommon (Nilsson *et al*, 1971). Our patient presented with gradual onset of fever, cough, and a progression of lower respiratory signs and symptoms diagnosed as mycoplasma pneumonia and confirmed by serology. Although the specificity of the particle agglutination test is not perfect, 12 of 139 (8.6%) serum samples gave positive titers while being negative by μ -capture ELISA and in-

direct immunofluorescence tests. There were concordant results with all three tests when particle agglutination tests gave titers of $\geq 1:1280$ (Barker *et al*, 1990). She subsequently developed seizure, bilateral pleural effusions, hemoconcentration, hemorrhagic manifestations, thrombocytopenia, and renal and hepatic failure, which could not be explained solely by *M. pneumoniae* infection. The patient fulfilled all four clinical diagnostic criteria of the WHO case definition of dengue hemorrhagic fever (DHF), *ie* fever, hemorrhagic manifestations, hepatomegaly, circulatory disturbances, and platelet count $\leq 100,000/\text{ml}$ with hemoconcentration (World Health Organization, 1986). Severe bleeding may complicate the clinical course in patients with DHF/DSS with prolonged shock and, frequently be the direct cause of death (Fagbami *et al*, 1995). Hepatomegaly was observed in 5-90% of DHF patients from various geographic areas. Elevated liver transaminase was reported in about 30-90% of DHF cases. Levels of aspartate aminotransferase are higher than those of alanine aminotransferase. Severe liver involvement may complicate the clinical picture of DHF, by causing liver failure and contributing to severe bleeding, and may potentiate the severity of disseminated intravascular coagulopathy (Lum *et al*, 1993). Acute renal failure related to the severity of renal hypoperfusion is an accompanying feature in most cases of dengue-associated liver failure. Seizures and brain edema in our patients may be the result of encephalopathy due the hepatic failure or dengue infection. The association of severe liver disease and encephalopathy has also been reported (Suvatte *et al*, 1990). The severity of neurological involvement associated with dengue infection is variable. More severe neurological manifestations are clinically indistinguishable from meningoencephalitis. A notable feature in a vast majority of patients with dengue encephalopathy is the lack of inflammatory response in the cerebrospinal fluid (CSF); however, there have been reports of CSF pleocytosis with normal glucose and protein (Lum *et al*, 1996). The pathophysiology of the neurological manifestations associated with dengue infection is still uncertain. The recovery of DEN-2 and DEN-3 viruses from the midbrain and CSF of patients in Myanmar and

Malaysia raises the possibility of the virus invading the brain, but this is not supported by pathological studies of the brain (Lum *et al*, 1996). Most patients with dengue encephalopathy recover without any residual neurological sequelae.

During *M. pneumoniae* infection, the production of autoantibodies to various tissues, including the lungs, smooth muscle, pancreas, and lymphocytes, has been observed (Biberfeld *et al*, 1976). Circulation of immune complex has been found early in the clinical course of *M. pneumoniae* infection (Biberfeld *et al*, 1974). Whether the immune response contributed to the severity of dual infections with dengue infection in our patient is not known. Early diagnosis and prompt treatment of unusual manifestations of dengue infection as coinfections in *M. pneumoniae* pneumonia may prevent serious adverse events and reduce the fatality rate.

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