UNUSUAL MANIFESTATIONS OF *MYCOPLASMA PNEUMONIAE* INFECTION IN CHILDREN

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ABSTRACT

Mycoplasma pneumoniae infection is no longer a benign condition it was originally thought to be. Many extrapulmonary manifestations affecting major organ systems like the central nervous system, cardiovascular system, haematological system, gastrointestinal system, musculoskeletal system and renal system have been described. Early recognition of these manifestations is often difficult and serological diagnosis may not be helpful. Three patients with large pleural effusions, encephalitis, hemiplegia, hepatitis, autoimmune haemolytic anaemia and renal failure are discussed to highlight the many varied presentations associated with this infection.

Keywords: *mycoplasma pneumoniae, extrapulmonary manifestations.*

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INTRODUCTION

Since the description of a pathogenic agent suspected to be the cause of primary atypical pneumonia in 1944 by Eaton[1] and its subsequent identification as a mycoplasma in 1962 by Chanock[2], *Mycoplasma pneumoniae* has emerged as a leading cause of respiratory tract infections in man.

The vast majority of clinically apparent *Mycoplasma pneumoniae* infections in children are respiratory illnesses without pneumonia, usually a minor febrile upper respiratory illness[3-7]. In fact, about 20% of infections due to this organism are completely asymptomatic[4,7] whilst clinically apparent pneumonia develops in only 3% to 10% of infected children[7]. However, severe respiratory diseases mimicking necrotising bacterial pneumonia, lung abscesses, Swyer-James syndrome, pneumatoceles and pleural effusions have been described[3,6-9].

Similarly, many extrapulmonary complications are now known to be associated with *Mycoplasma pneumoniae* infections. Complications involving other major organ systems eg the central nervous system, haematological, cardiovascular and renal systems are well documented [3,5,7,10-29]. In addition, involvement of the skin, muscles and joints have also been described[3,5,7,30-32].

Although the successful use of erythromycin in ameliorating the respiratory symptoms caused by this organism is well documented[33-36], its role in the treatment of these extrapulmonary complications remain questionable as they are thought to be immunologically mediated [3-8,10,13,15,18,23,25-29]

The purpose of this report is to highlight the protean manifestations of *Mycoplasma pneumoniae* infections in children.

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CASE 1

MS, a 6-year-old Malay boy, was admitted to Tan Tock Seng Hospital in July 1987 for fever of 6 days and a dry cough of 2 days duration. Upon admission, he was febrile and toxic looking. Chest X-ray showed right perihilar opacities (Fig 1). Although his lungs were clinically clear, a diagnosis of chest infection was made and ampicillin started. There was however no clinical improvement and he remained febrile over the next 5 days. Ten days from the onset of his respiratory symptoms, he developed three major clinical problems:

(i) He threw a grand-mal seizure one week after admission and became drowsy (coma III) post-ictally. There was no focal neurological deficit. A clinical diagnosis of encephalitis was made but a lumbar puncture was refused by the parents. Intravenous ampicillin, gentamicin and

Fig 1 - Chest X-ray of MS on admission

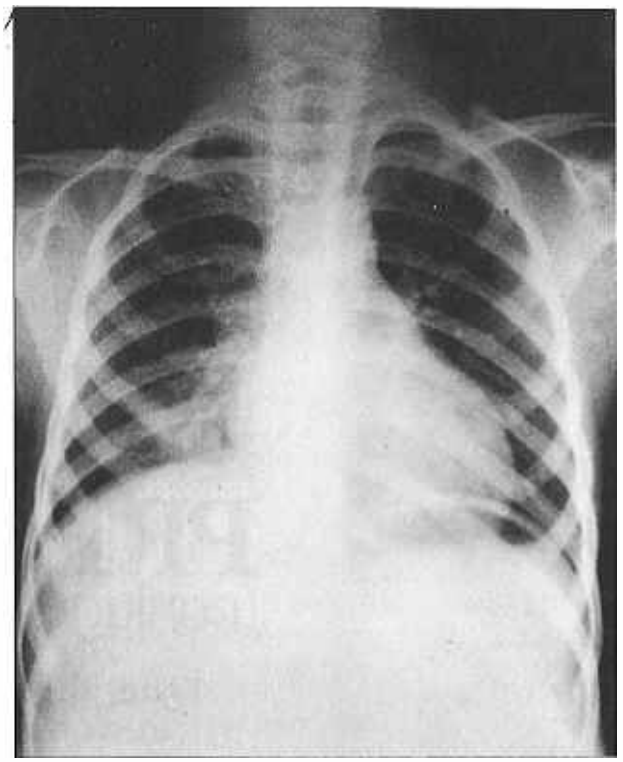
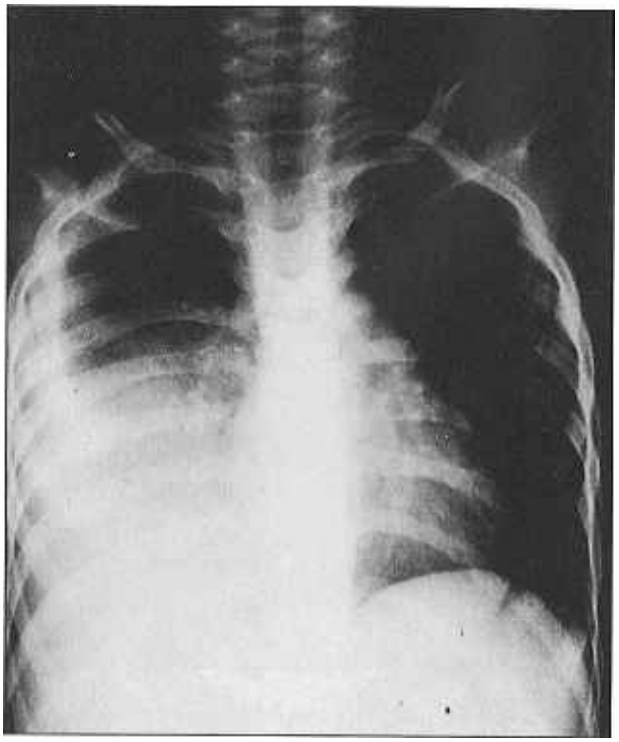


Fig 2 - Chest X-ray of MS showing recurrence of the effusion 3 days after the first aspiration



ceftriaxone were started. An urgent cranial CT scan showed cerebral edema and electroencephalogram result was consistent with an encephalitis. The patient subsequently developed multiple recurrent left-sided seizures requiring high doses of phenobarbitone and diazepam before adequate control was achieved. His conscious state started to improve 3 days later. Consent for lumbar puncture was then obtained and the cerebrospinal fluid biochemistry were as follows: cell count 1, glucose 62mg/dl, total protein 20 mg/dl, globulin negative. The gram stain smear, culture, latex co-agglutination and viral studies were negative. His conscious state continued to improve and he became completely conscious and rational 5 days from the onset of the first seizure.

(ii) Concurrent with the first seizure, MS also developed signs of a right-sided pleural effusion. Pleural tap yielded 25 ml of straw coloured serous fluid and analysis revealed: specific gravity 1.026, total protein 2.5 gm/dl and 80% lymphocytes. Gram stain smears for acid-fast bacilli, bacterial cultures, cultures for mycobacterium tuberculosis were negative. However, the effusion recurred requiring repeated aspirations (Fig 2). Mantoux test was non-reactive and CT scan of the lungs and abdomen showed a right-sided effusion and mild hepatomegaly. No focal lesions were seen. A lung biopsy done 3 weeks later showed mainly inflammatory changes.

Serological studies for influenza A, B, adenovirus, parainfluenza 1,2,3, cytomegalovirus, legionella and psittacosis were negative. Repeated blood cultures (on a total of 6 different occasions) and Widal Weil Felix serology were negative. Rheumatoid factor and anti-nuclear antibody were also negative. The only positive serology was that of *Mycoplasma pneumoniae*

The complement fixation titres were :

1 : 28 (1 week after admission)
1 : 1024 (2 weeks after admission), and
1 : 2048 (3 weeks after admission)

Even after discharge, the titres remained high (1:512 one month after onset and > 1:128 one year later). In view of the attendant delay in obtaining these results, erythromycin was started only 36 days after admission. All other antibiotics were then stopped. His fever subsided dramatically 2 days later. The pleural effusion however, only showed significant radiological resolution about 5 months after discharge.

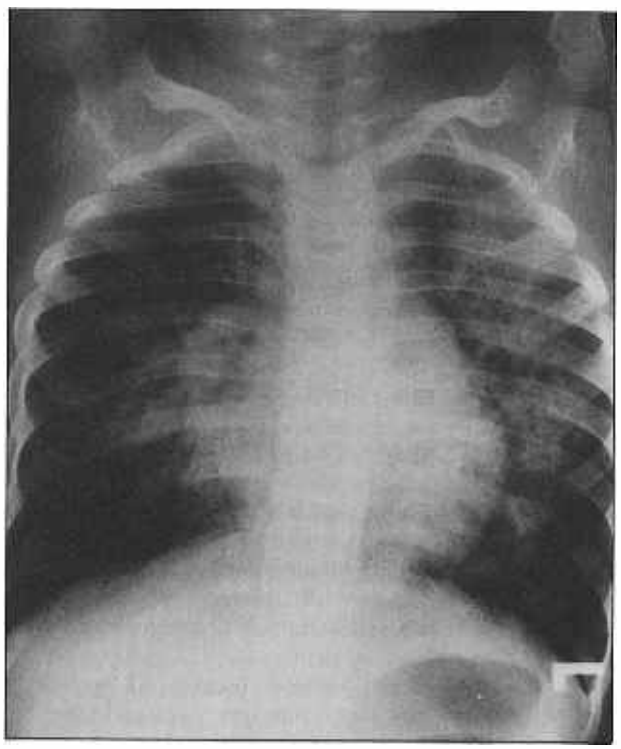
(iii)Ten days after admission, MS was also noted to be jaundiced with hepatomegaly (5 cm below the right costal margin). Liver function tests were consistent with hepatitis (SGPT 782 U/L, SGOT 202 U/L). Jaundice resolved spontaneously over the next few days and the serum transaminases also showed a gradual improvement (SGPT 115 U/L, SGOT 60 U/L one week later and SGPT 65 U/L, SGOT 83 U/L two weeks later).

In summary, this patient developed serologically confirmed *Mycoplasma pneumoniae* with features of massive, persistent pleural effusion, encephalitis and hepatitis. There has been no obvious sequelae to date.

CASE 2

RBR, a 6-year-old Malay boy with Down Syndrome, was admitted to Tan Tock Seng Hospital in January 1991 with a 6-day history of fever and cough. He had a past history of iron-deficient anaemia at the age of 1 year for which i/v erythrocytes and iron supplement were given. Upon admission, he was febrile with bilateral lung crepitations and hepatomegaly (3 cm below the right costal margin). Chest X-ray showed ill-defined bilateral perihilar opacities and a diagnosis of infection was made (Fig 3). White cell count was 11,800 /mm^3, haemoglobin 7.8 gm/dl (RBCs mainly

Fig 3 - Chest X-ray of RBR on admission



hypochromic, microcytic with a few spherocytes), blood urea 23 gm/dl and creatinine 0.8gm/dl. Ampicillin was started.

Cloxacillin and gentamicin were added 3 days later as he remained febrile and toxic-looking. Blood and sputum cultures were negative. Complement fixation antibodies to *Mycoplasma pneumoniae* returned as >1:128. Ampicillin and cloxacillin were then stopped and erythromycin started. Unfortunately, he remained febrile and ill. One week after admission, he became pale, edematous and was more tachypneic. Haematological investigations showed autoimmune haemolytic anaemia with renal failure (Hb 6.1 gm/dl, reticulocyte count 5.5% peripheral blood film showed RBC agglutination, Direct Coombs test +++, anti-E and auto anti-I antibodies and haemoglobinuria present, blood urea 151 mg/dl and creatinine 6.8 gm/dl). Ultrasound of the kidneys was normal.

RBR remained on erythromycin but gentamicin was replaced with ceftriaxone. The acute renal failure was managed conservatively with fluid and protein restriction, resonium A and calcium supplements. The serum creatinine continued to climb to a peak of 10.7 mg/dl one week from the onset of renal failure. Concurrently, his urine output decreased to 0.5 ml/kg/hr. It was one week later that the urine output improved together with corresponding decline in serum creatinine levels.

RBR's haemoglobin level also showed a precipitous drop to a low of 4.2 gm/dl five days after onset of haemolytic anaemia. There was difficulty in obtaining compatible blood for transfusion because of the presence of antibodies. One unit of the most compatible blood was finally given and his subsequent haemoglobin was maintained at >8 gm/dl. Direct Coombs test became negative 6 days from the onset. Table I summarises his haematological and biochemical progression. Follow-up haemoglobin levels after discharge showed a

Table I - RBR's haemotological and biochemical progression whilst in hospital

Days of hospitalisation	1	9	13	42
Hb (gm/dl)	7.8	6.4	4.3	8.8
WBC (mm^3)	11800	21600	13800	11400
Platelet (x1000mm^3)	490	75	105	295
Retic (%)	-	5.5	8	-
Urea (mg/dl)	23	198	249	66
Creatinine (mg/dl)	0.8	8.3	7.4	2.3
I/V erythrocytes			1 unit	

gradual increase to 11.3 gm/dl with a reticulocyte count of 1% 6 months later.

Three weeks after hospitalisation, a chest X-ray was repeated to assess the progress. This showed pneumonia consolidation in both lung fields with a lobar pneumonia in the right lower zone and a moderate size right-sided pleural effusion (Fig 4). At this juncture, he was already afebrile although crepitations were still present over both lungs. Complete radiological resolution only occurred about 1 year later.

In summary, RBR showed features of a severe *mycoplasma pneumoniae* infection complicated by

Fig 4 - Chest X-ray of RBR 3 weeks later

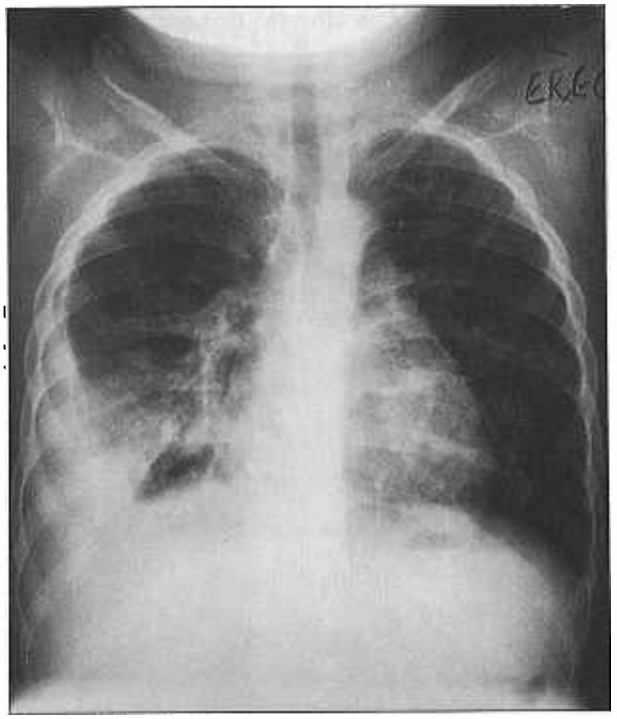
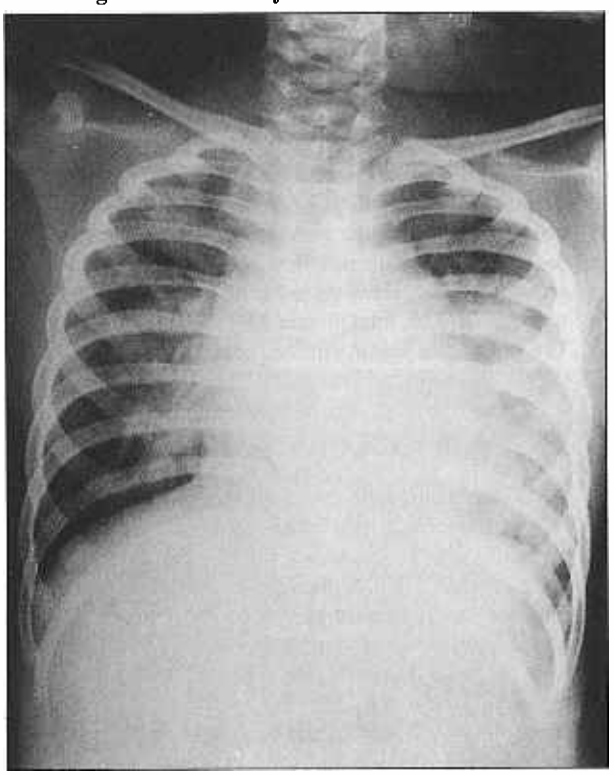


Fig 5 - Chest X-ray of NBM on admission



autoimmune haemolytic anaemia, renal failure and persistent pleural effusion.

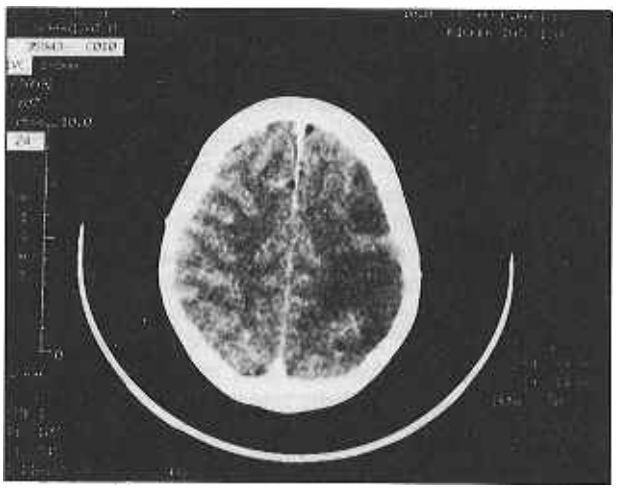
CASE 3

NBM, a 4-year-old Malay girl with Down Syndrome, was admitted to Tan Tock Seng Hospital in January 1992. She presented with acute breathlessness and right-sided weakness together with a week's history of fever and productive cough. On admission she was febrile and in respiratory distress. There were bilateral rhonchi and crepitations in the lungs as well as right upper motor neuron facial nerve palsy with a dense

right hemiplegia.

Chest X-ray showed bilateral patchy opacities consistent with infection (Fig 5). The white cell count was raised, 17,900 /mm^3 with 75% polymorphic predominance. The *Mycoplasma pneumoniae* complement fixation antibody titre was >1:128. A convalescent titre done 6 weeks later was still >1:128. Blood and sputum cultures were negative. Cranial CT scan revealed a recent left cerebral infarct in the middle cerebral artery territory (Fig 6). Two-D echocardiography did not reveal any structural cardiac abnormalities.

Fig 6 - Cranial CT scan of NBM showing left cerebral infarct



She deteriorated several hours after admission with Type II respiratory failure requiring mechanical ventilation. She was ventilated for 48 hours and was gradually weaned off onto a headbox oxygen with 0.5 FiO_2. Oxygen therapy was gradually weaned off over the next week. Serial chest X-rays subsequently showed resolution of infective changes.

NBM was treated initially with ampicillin and gentamicin for 4 days and erythromycin for 2 weeks when the mycoplasma titre was known. At review, one week after discharge, there was persistence of the facial nerve palsy and right hemiplegia.

In summary this patient had severe *mycoplasma pneumoniae* infection complicated by respiratory failure, facial nerve palsy and hemiplegia.

DISCUSSION

Mycoplasma pneumoniae infections occur most frequently between the ages of 5 and 30 years and are rare before the school-going age[5,37]. Infections occurring in the very young tend to be either mild or asymptomatic[38]. There appears to be a slight male preponderance[5]. Extrapulmonary complications have been demonstrated to occur in as high as 45% of documented infections[7]. Our three patients are just before the school going age and are all Malays. This apparent racial predilection may be coincidental as at present there has not been any documented racial pre-dilection in the development of extrapulmonary complications. However, it has been reported that central nervous system manifestations, which appear to be the commonest of these complications, tend to show a male predominance, especially in the younger age groups[13].

Contrary to earlier held beliefs that *Mycoplasma pneumoniae* only produced mild upper respiratory tract infections[3-7], our patients had fairly severe respiratory symptoms with one requiring ventilation. Similarly, the rarity of pleural effusions in *Mycoplasma pneumoniae* infections had been emphasised in earlier papers to such an extent that it has been suggested that its presence in a patient should make one suspect another diagnosis[39]. This has since been shown to be untrue and small effusions can be demonstrated in at least 20% of patients with the use of lateral decubitus chest X-rays[3,8,9,40]. What is equally important is the protracted nature of these effusions despite pleural aspirations and erythromycin therapy. In our first patient, MS, the effusion showed radiological resolution only 5 months later and kept recurring despite repeated aspirations. In our second patient RBR effusion took one year to resolve although we did not aspirate it as he was asymptomatic.

Present studies indicate that symptoms and clinical findings are not useful in predicting which patients will develop an effusion[9]. Large pleural effusions associated with *Mycoplasma pneumoniae* infection continue to be regarded as rare and in those reported, there was concurrence with our cases in that there was slow but complete resolution of the effusions[3,22].

While some authors have asserted that erythromycin accelerated the resolution of roentgenographic abnormalities, we found this to be untrue in our patients. Our patients, MS and RBR, took 5 months and at least 3 weeks for clinical and radiological resolution of the pleural effusions. Yet in RBR, the pleural effusion lasted even longer. The lack of efficacy of erythromycin may actually be consistent with the theory that these pleural effusions are the result of indirect immunologic injury rather than direct microbial injury[4,7].

Neurological complications associated with *Mycoplasma pneumoniae* infections have been recognised as early as 1938[41]. Since then many of the following manifestations have been reported viz encephalitis, meningoencephalitis, polyradiculitis, aseptic meningitis, acute cerebellar ataxia, cranial nerve palsies, psychosis, transverse myelitis, peripheral neuropathy, mononeuritis multiplex, hemiplegia and granulomatous cerebral angiitis [3,5,7,10-19,42,43]. Most of these have a high morbidity and mortality[10,13]. Our first patient developed encephalitis with seizures about 2 weeks from onset of illness and very rapidly became comatose. His clinical picture is very similar to those patients described by Behan[10], an entity described as Acute Disseminated Encephalomyelitis (ADEM), who presented with nonspecific symptoms like fever, headache, vomiting and then rapidly developed features of sensorial disturbance seizures and focal signs. Our patient MS, recovered full consciousness 5 days later and to date has not exhibited any gross neurological impairment. The third patient, NBM, developed an isolated seventh cranial nerve palsy and a dense hemiplegia. Two of Behan's patients had dense hemiplegia and one had bilateral facial nerve palsies[10]. Hemiplegias and cranial nerve mononeuropathy are now being increasingly reported in association with *Mycoplasma pneumoniae* infection[3,10,13,15,17].

The pathogenesis of these CNS manifestations remain unclear although various hypotheses have been suggested. As early as 1966 neurotoxins have been implicated and although other mycoplasma species pathogenic to animals have been demonstrated to produce neurotoxins, such has not been the case so far for *Mycoplasma pneumoniae*[13]. Intravascular thrombosis of the vessels in the CNS has also been suggested and in fact confirmed in post-mortem findings of one fatal case[14].

Direct invasion of the CNS by the organism has also been suggested. Although in some cases, actual isolation of the organism was successful, other similar attempts have

failed[13,15]. The most attractive possibility is an autoimmune process. The lag period between the onset of respiratory and CNS symptoms is supportive of this. In our patients, there was a lag period of 1 week to 10 days. Antibodies against brain tissue have been identified[7,13].

Some authors have postulated that CNS involvement is due to an autoimmune process and have used steroids in an attempt to suppress it. In Behan's[10] patients, 2 were given steroids and one patient, ACTH. All three did not exhibit any dramatic neurological improvement. Larer[17] described the use of steroids in three patients. One apparently had improvement of neurological symptoms whilst in the other two, no appreciable difference was noted. Clearly, the use of steroids in such patients remain controversial until the exact pathogenesis of these CNS manifestations have been elucidated.

Autoimmune haemolytic anaemia was first described by Barret-Connor in his review of 50 cases of *Mycoplasma pneumoniae*. Haemolysis usually occurs two to three weeks after onset of illness and coincides with recovery from pneumonia. In RBR's case clinically apparent haemolysis began about 2 weeks after onset and lasted 6 days.

Fortunately, most recover spontaneously. A positive direct Coomb's test occurs in 83% of patients[3] and cold agglutination occurs in about 76% of patients[3]. This autoantibody appears to be specific for I antigen on the RBC surface[7]. A strongly positive Coomb's test and presence of auto anti-I antibodies were strong supportive evidence of a *Mycoplasma pneumoniae* induced haemolytic anaemia in our patient RBR. Renal failure, as in this patient, has been reported in association with this cold agglutinin response[42].

Hepatitis[3] and pancreatitis[3,7,27,28] are also associated with this infection. Most of the enzymatic derangement in hepatitis is transient and self limiting[7]. In our first patient, there was spontaneous recovery within one week.

Host factors are important in the pathogenesis of Mycoplasma disease[8]. A more severe disease occurs in patients with haemoglobinopathies[21,22] and in patients with immune-deficiency syndromes[8,43]. Suggestions have been made that the subtle interplay between the organism and host's lymphoid cells result in the diverse clinical manifestation seen[7,8,13,44,45].

Making a diagnosis of *Mycoplasma pneumoniae* infection early in the illness can be difficult. Culture for *mycoplasma pneumoniae* is not routinely available in our laboratories. Furthermore, culture results take at least 10 days to be confirmed[3,5]. Serologic tests are of substantial diagnostic value but usually only in a retrospective way. A more than fourfold rise of complement fixation antibody in paired samples of sera is confirmation of infection. Complement fixation titres of antibodies begin to rise about seven to nine days after infection and peak at three to four weeks. These remain at peak levels for four to six months after which there is a gradual fall to minimal levels (<1:16) in two to three years time[3].

In the presence of supportive clinical features, a single titre of > 1:128 in the acute sera is generally acccpted as presumptive evidence of infection. However, in patients presenting with uncommon features, a high complement fixation titre of antibodies to *Mycoplasma pneumoniae* infection could be due to a past infection. Another problem lies in the organism's lipid antigen having antigenic properties in common with human brain tissue. It is possible that a lesion in the CNS caused by other agents may release antigen related to *Mycoplasma pneumoniae* lipid antigen. This could lead to an antibody response and a cross-reaction in the complement fixation test, thus giving a false positive serological diagnosis[12,13,46,47].

Cold agglutinins have been reported to be positive in 33% to 76% of patients with active infection[3]. However, although readily available and relatively immediate in their diagnostic value, they are nonspecific and may develop in patients with infectious mononucleosis, rubella, adenovirus and influenza virus[3,24]. In general, therefore, a diagnosis of *Mycoplasma pneumoniae* infection is best made clinically with serological evidence as supportive indices.

Since the first reported successful use of demethylchlortetracycline in 1961 in reducing the morbidity of the illness[6], tetracyclines and erythromycin have been accepted as effective antibiotics in the treatment of the respiratory symptoms. Of the two, erythromycin has been shown to be superior in that fever and severity of cough were reduced more quickly[33-35]. However, resistance of *Mycoplasma pnemoniae* to this antibiotic has appeared[36,48]. Furthermore, although erythromycin relieves the symptoms, it does not eradicate the organism in experimental studies[6]. The prophylactic use of this antibiotic, as well as tetracyclines, has also been questioned[6]. Whatever the case may be, erythromycin has not been shown conclusively to be beneficial in the treatment of the extrapulmonary manifestations[5,17]. We found this to be true in our patients as well. There have been others, however, who had reported beneficial effects[10].

Finally, although antibiotics may be effective in reducing the morbidity associated with *Mycoplasma pneumoniae* infections, they may not be the answer to the control of these infections. Vaccines, both inactivated and live attenuated ones, have been shown to have protective value[6]. However, although up to 83% of vaccines have been shown to develop significant antibody titres which protected them against subsequent infections, those who did not convert manifested a more severe clinical illness upon subscquent challenge. This is due possibly to prior sensitisation to the inactivated organism[6].

Clearly, more research into these vaccines as well as better understanding of the pathogenesis of the extrapulmonary manifestations associated with *Mycoplasma pneumoniae* infections is required before their prevention and treatment could be rationalised. To this end, early clinical recognition of these manifestations is an important first step.

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