

Case Report

Extra-Pulmonary *Mycoplasma pneumoniae* Infection in a Healthy 25-Year-Old Female: A Case Report

Minna Chang*

Imperial College, 72 Coventon Road, SW17 0QN, London

*Corresponding author: Minna Chang, Imperial College, 72 Coventon Road, SW17 0QN, London

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Summary

Here we report a case of *Mycoplasma pneumoniae* (*M. pneumoniae*) infection in a young, previously fit and healthy female, consisting of multi-system manifestations but no pulmonary symptoms at time of presentation. *M. pneumoniae* was confirmed by serology testing. The patient made a full recovery after 6 weeks. Simultaneous presentation of acute hepatitis, neutropenia, thrombocytopenia, erythema multiforme, arthralgia, and vomiting is rare and to our knowledge, this is the first case report of this presentation.

Abstract

Introduction: *M. pneumoniae* is a respiratory pathogen, which commonly causes upper and lower respiratory infections. It primarily affects children and young adults. Respiratory symptoms are well recognised, but extrapulmonary involvement is also common. Other systems that have been implicated in the disease include: skin, mucus membranes, central and peripheral nervous systems, cardiovascular, haematological, renal, musculoskeletal systems. Here, we report a case of an otherwise healthy, young female with *M. pneumoniae*, who presented with right upper quadrant abdominal pain.

Case presentation: A healthy 25-year-old female was referred to A&E by her general practitioner, after presenting with fever, malaise and right upper quadrant pain. *M. pneumoniae* was confirmed retrospectively by serology. The patient made a full recovery after a six-day course of doxycycline 100 mg.

Conclusion: *M. pneumoniae* is a well-established cause of respiratory infections in children and young adults. A febrile illness with multisystem involvement, even in the absence of respiratory symptoms, should raise suspicion of *M. pneumoniae* infection in healthy, young adults. Our case illustrates the multi-system involvement of *M. pneumoniae*, which was initially missed, due to paucity of respiratory symptoms at presentation.

Introduction

M. pneumoniae is a respiratory pathogen in the class of Mollicutes, which commonly causes upper and lower respiratory tract infection. The bacterium lacks a cell wall and is the smallest self-replicating organism in nature [1-4]. *M. pneumoniae* is most commonly seen in children and young adults and is transmitted by cough and aerosols, with infected individuals carrying the organism in the nose, trachea and sputum [4]. It has an incubation period of 1-3 weeks and is reported to represent ~15-20% of community acquired pneumonias in adults [2,4]. In England, epidemics peak roughly every 4 years, with the highest prevalence amongst 5-14 year olds [1].

Common upper respiratory tract manifestations include a sore throat, hoarseness, fever, cough, coryza and malaise. Lower respiratory tract infections may manifest with dyspnoea, wheezing and in severe cases, respiratory failure [4].

Extra-pulmonary organ involvement, which have been implicated include cardiovascular, gastrointestinal, haematological, dermatological, renal, musculoskeletal, ocular and neurological systems [1-3]. The exact incidence of extra-pulmonary manifestations is unknown, but some reports estimate that these may occur in up to 25% of cases [1].

A systemic presentation involving several organ systems, with no pulmonary symptoms at presentation, has rarely been reported. We report a case of *M. pneumoniae* in a previously healthy individual, with no pulmonary symptoms at presentation, but manifested extra-pulmonary symptoms involving several organ systems. Furthermore, routine bloods demonstrated neutropenia, which is an extremely rare extra-pulmonary finding associated with *M. pneumoniae*.

Case Presentation

A 25 year-old female medical student was referred to A&E by her general practitioner for nausea, vomiting, fever and Right Upper Quadrant (RUQ) pain. The patient complained of a febrile illness, which started 10 days ago, with right upper quadrant pain, which started 24 hours before presentation. The patient's symptoms initially began with severe headache, photophobia, nausea and one episode of vomiting. These settled overnight and were replaced by a fever that spiked at 40.3°C with malaise, myalgia, tiredness and nausea.

On examination, there was no cough, coryza or pharyngeal changes. Abdominal examination revealed guarding in the right upper quadrant of the abdomen, but spleen and liver were not palpable. The pain was worse on lying down and leaning to the ipsilateral side.

Past medical history included polycystic ovarian syndrome. There was no recent history of travel, vaccinations were all up to date, and to her knowledge, the patient had not been in contact with unwell individuals. The patient was taking regular ibuprofen and paracetamol for symptomatic relief.

On presentation to A&E, the patient was afebrile at 37.3°C, heart rate 97/min, respiratory rate 18/min, blood pressure 110/80 and oxygen saturation 96% on room air. She was alert and comfortable at rest. General examination revealed no pallor, icterus or lymphadenopathy. Throat examination was unremarkable and chest was clear, with equal entry on both sides.

Urine analysis showed very dark urine, with ketones 2+, trace blood and leukocytes+. The patient was treated for suspected cholecystitis with intravenous fluids, antibiotics and analgesia.

Laboratory testing on initial admission demonstrated: white blood cells $2.5 \times 10^9/L$, platelets $137 \times 10^9/L$, CRP 38 mg/L, bilirubin 14 $\mu\text{mol/L}$, ALT 83 IU/L, ALP 162 IU/L. Blood tests 3 days later demonstrated a further fall in white blood cells and platelets: white blood cells $3 \times 10^9/L$, neutrophils $0.5 \times 10^9/L$ and platelets $100 \times 10^9/L$. On the other hand, hepatic enzymes rose, demonstrating: ALT 294 IU/L and ALP 197 IU/L, GGT 106 IU/L. CRP was 18 mg/L.

Liver Ultrasound Demonstrated No Stones or Cholecystitis

On day 4 of admission, the patient developed a patchy, erythematous rash on her chest, which was neither itchy nor painful. The patient complained of new-onset breathlessness, so a chest X-ray was performed. This was unremarkable. In light of a raised D-dimer and breathlessness, a CTPA was carried out. This demonstrated ground glass opacities in the right lower lobe, prominent hilar lymphadenopathy and multiple sub-centimetre axillary nodes.

A blood film demonstrated reactive lymphocytes and platelet anisocytosis, consistent with a viral infection. Viral screen was negative for HIV, Hepatitis B, Hepatitis C and Hepatitis A. It also demonstrated prior infection with CMV and EBV, but no evidence of acute infection.

A diagnosis of an unspecified viral infection was made. After 3 days, the patient was able to tolerate oral fluids. Blood tests demonstrated an increase in platelets, white blood cells and neutrophil count, with a decline in liver enzymes and CRP. The patient was discharged with a course of oral doxycycline (100 mg per day for 6 days).

Based on the clinical presentation and later serology, a diagnosis of *M. pneumoniae* was made retrospectively. The patient developed polyarthralgia, enthesopathy and a widespread erythematous rash, consistent with erythema multiforme. These were treated with ibuprofen and 0.1% topical mometasone cream, applied twice a day. The rash responded well to the steroid, and the arthralgia and enthesopathy resolved after 2-3 weeks. The patient made a full and uneventful recovery.

Discussion

We illustrate a case of serologically confirmed *M. pneumoniae*, which manifested with predominantly extra-pulmonary symptoms. To our knowledge, this is the only reported case presenting with

acute hepatitis, bicytopenia (neutropenia and thrombocytopenia), erythema multiforme, arthralgia, and vomiting.

Previously reported extra-pulmonary manifestations include cardiovascular (pericarditis, endocarditis, myocarditis, cardiac thrombi), hepatic, haematological (autoimmune haemolytic anaemia, thrombocytopenic purpura, disseminated intravascular coagulation), dermatological (erythema nodosum, cutaneous vasculitis, erythema multiforme, Steven-Johnsons Syndrome), glomerulonephritis, arthritis, conjunctivitis and neurological symptoms (encephalitis, meningitis, Guillain Barre syndrome) [1-3]. These manifestations may occur before, during or after resolution of respiratory symptoms and usually fully resolve 2-3 weeks after eradication of the respiratory disease. Respiratory symptoms may be minimal or even absent [1-3].

The exact incidence of extra-pulmonary manifestations is unknown, but some reports estimate that these occur in up to 25% of cases [1].

The mechanism behind extrapulmonary involvement remains incompletely understood. Various theories have been postulated, including:

- 1) direct attack from the bacterium, involving damage due to host cytokines (especially interleukin-6 and interleukin-8) and secretion of toxic molecules and proteins by the bacterium (including H_2O_2 and nucleases) [2,4,5]
- 2) an indirect autoimmune attack by antibodies and immune complexes [2,4,5],
- 3) vascular occlusion involving vasculitis and/or thrombosis [2,4,5],
- 4) molecular mimicry between mycoplasma cell wall components and host tissues [2,4].
- 5) It has also been suggested that some manifestations may be the result of post-infectious inflammation [4].

In vitro studies have shown that *M. pneumoniae* can adhere to red blood cells, which may promote dissemination of the organism into other tissues [5].

Our patient developed lymphopenia ($0.3 \times 10^9/L$) and neutropenia ($0.5 \times 10^9/L$), which were noted on the day of admission. Whilst haemolytic anaemia has been well documented [1-7], *M. pneumoniae* associated neutropenia and leukopenia remain extremely rare. To our knowledge, there are currently only 3 other published case reports of this phenomenon and no such phenomenon in an otherwise healthy, young adult.

Barge et al. [8] report a case of an 85-year-old male with exacerbation of COPD and positive serological test for *M. pneumoniae*. The patient developed transient agranulocytosis. Granulocyte autoantibody testing showed positive IgG and IgM autoantibodies against neutrophils. This was found to produce significant agglutination. The agranulocytosis responded well to granulocyte colony-stimulating factor and the infection was successfully treated with azithromycin. Like our patient, L. Barge et al. describe a mild thrombocytopenia relative to the neutropenia.

The main mechanisms postulated for the haematological manifestations is antibody cross reaction with red blood cells, platelets and white blood cells. The detection of antibodies in patients' serum supports such autoimmune mechanism [8].

Chen et al. [9] report a case of a 4-year-old, who presented with upper respiratory tract infection symptoms. Serological testing demonstrated *M. pneumoniae*. The patient was also found to have neutropenia, thrombocytopenia and acute hepatitis. Despite normal haemoglobin on laboratory testing, erythrocyte-bound C3d was strongly positive, as was Coomb's test. The team also found antiplatelet and antineutrophil antibodies.

Haemolytic anaemia in *M. pneumoniae* is thought to be due to cold agglutinins [8]. Usually IgM antibodies, these bind to the erythrocyte cell membrane at temperatures below 5°C. This leads to agglutination and haemolysis of the cell, precipitating anaemia. Our patient was not tested for these antibodies.

Thrombocytopenia associated with *M. pneumoniae* is thought to be due to two main mechanisms: thrombotic thrombocytopenic purpura and direct antibody effects [9]. Chen et al. report a case of *M. pneumoniae* associated with anti-platelet antibodies and thrombocytopenia. These antibodies were directly associated with platelets. The finding of increased megakaryocyte count in the patient's bone marrow suggested increased peripheral platelet destruction and thus further supported an autoimmune mechanism.

To our knowledge, this is the first report of neutropenia with a systemic manifestation of *M. pneumoniae* infection. These findings may further our understanding of the heterogenous presentation of the infection.

Our patient also developed transient transaminitis, in keeping with an acute hepatitis picture. This has been estimated to occur in 2-21% of cases [3]. Changes in hepatic enzymes are usually transient, with complete recovery after eradication of the organism. The exact pathogenesis of *M. pneumoniae*-induced hepatitis is still not understood, but the major mechanisms that are thought to be implicated include molecular mimicry between mycoplasma cell components and hepatic cell surface molecules and direct invasion of the liver by the pathogen [2,4]. It has been further suggested that early-onset hepatitis may be more likely due to direct mechanisms, whereas late-onset hepatitis may be more likely due to vascular injury [5].

Skin changes may be seen in 10%-25% of cases and is thought to be due to a combination of immune complex-mediated vascular injury, cell-mediated damage and autoimmune mechanisms [4,6]. Cutaneous manifestations are heterogeneous and can be confluent or confined to specific areas. Most common cutaneous presentations include maculopapular, vesicular, erythema multiforme and urticarial lesions [1-3,6]. These are generally self-limiting and associated with excellent clinical prognosis. Rarer and more serious presentations include Stevens-Johnson syndrome and toxic epidermal necrolysis [6].

The pathogenesis of cutaneous manifestations associated with *M. pneumoniae* is not fully understood, but some have postulated a combination of mechanisms including type III immunological hypersensitivity, immune complex deposition and immune cell

infiltration, fragmentation and nuclear debris deposition [6]. Another mechanism has suggested a micro-vessel disease involving multiple thrombi and cold agglutinins [6]. *M. pneumoniae* has also been isolated from the cutaneous lesions, suggesting involvement of a direct mechanism [5].

The majority of *M. pneumoniae*-associated dermatological conditions respond to eradication of the bacterium and topical steroids. Commonly used antibiotics to treat *M. pneumoniae* include erythromycin, azithromycin and co-amoxiclav. All of these have been associated with cutaneous eruptions and it can therefore be difficult to determine whether the eruptions are due to the bacterium or indeed the antibiotics. Our patient developed widespread erythema multiforme, which responded well to 0.1% topical mometasone cream, applied twice a day.

Conclusion

In conclusion, we report a multi-system presentation of *M. pneumoniae* presenting with acute hepatitis, leukopenia, neutropenia, erythema multiforme, arthralgia, and vomiting. There was a remarkable absence of respiratory symptoms at primary presentation. *M. pneumoniae* is a common pathogen affecting children and young adults. It should be considered as a differential diagnosis in a febrile young patient with multisystem involvement, even in the absence of respiratory symptoms.

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