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SHORT COMMUNICATION

Mycoplasma pneumoniae infection associated with urticarial vasculitis mimicking adult-onset Still's disease

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Abstract *Mycoplasma pneumoniae* is well known to be a frequent cause of atypical pneumonia worldwide. However, it may also present with a wide variety of clinical features, including cutaneous symptoms, which are not widely recognised. Urticarial vasculitis occurring with *M. pneumoniae* has been described to occur in only one other case report. This amalgamation of non-specific clinical symptoms and signs can lead to a diagnostic dilemma. We describe a case of *M. pneumoniae* infection presenting with extrapulmonary manifestations and urticarial vasculitis, which was misdiagnosed as adult-onset Still's disease (AOSD). Had immunosuppressive therapy been commenced for AOSD in the presence of undiagnosed infection, this may have resulted in potentially serious consequences. This case highlights the need to remain vigilant about diagnosing *M. pneumoniae* as its serological diagnosis may take weeks and it has many extrapulmonary manifestations, which can masquerade as other conditions.

Keywords *Mycoplasma pneumoniae* · Infection · Urticaria · Vasculitis · Still's disease · Adult onset

Introduction

Mycoplasma pneumoniae is a common bacterial pathogen in young adults and children, spread by respiratory droplets. However, it may present with a wide variety of non-specific clinical manifestations, which can lead to misdiagnosis, and it has potential to cause significant morbidity. Urticarial vasculitis (UV) is a rare cutaneous vasculitis. It presents with skin wheals that resemble urticaria; however, on histological examination, small vessel vasculitis is seen. UV is most commonly idiopathic, but it has been associated with infections such as hepatitis A, B and C, Epstein–Barr virus and *Borrelia burgdorferi*; medications such as ACE inhibitors, penicillin, sulphonamides; neoplasia; and connective tissue disorders such as systemic lupus erythematosus and Sjogren's disease [1]. However, to the best of our knowledge, only one report in the literature has previously described UV in association with *M. pneumoniae* [2].

We present a unique case of UV occurring in association with *M. pneumonia,* which is manifested with extrapulmonary symptoms without pneumonia. This resulted in clinical features mimicking adult-onset Still's disease (AOSD).

Case history

A previously well 38-year-old Malaysian hairdresser presented with a 2-week history of sore throat and fever. She also had a non-productive cough and generalised arthralgia. Her past medical history included hypertension and type 2 diabetes mellitus for which she was taking metformin and amlodipine. She had no recent travel history and had never been in a sexual relationship.

On examination, she had a widespread, maculopapular erythematous, non-evanescent rash, which was pruritic, burning in nature and changed position daily (see Fig. 1). She was febrile (temperature 40°C). She had no active

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synovitis, and systemic examination was otherwise unremarkable.

Laboratory tests revealed haemoglobin 13 g/dl, white cell count 19 × 10^9/l, neutrophils 17.7 × 10^9/l, C-reactive protein 423 mg/l, erythrocyte sedimentation ratio 121 mm/h, alkaline phosphatase 174 iu/l, alanine transaminase 49 iu/l and ferritin level 14,487 g/l. She had a low C4 of 0.11 (normal range 0.14–0.54) and normal C3 level of 0.99. Bone profile, renal function, immunoglobulins and protein electrophoresis were normal. Urine dipstick was normal.

Blood, urine, stool cultures and throat swabs were negative. Autoimmune (ANA, ANCA, RF and CCP) and virology screen (H1N1, adenovirus DNA, parainfluenza RNA, parvovirus, CMV and EBV) were negative. Tests for measles, anti-streptolysin O titre, hepatitis serology, syphilis, tuberculosis, HIV and genitourinary swabs were also negative. Chest radiograph, chest/abdominal/pelvic computed tomography and echocardiogram were normal.

Fever, arthralgia, sore throat, rash and raised inflammatory markers persisted despite a 7-day empirical course of intravenous co-amoxiclav and antihistamines. A rheumatological opinion was then sought due to a persistent fever of unknown origin for over 3 weeks. She fulfilled the criteria for adult-onset Still's disease according to the Yamaguchi criteria (see Table 1) and was initially commenced on ibuprofen. The following week, her fever and symptoms resolved and inflammatory markers halved.

Following dermatology review, a skin biopsy was performed, revealing superficial perivascular inflammatory cell infiltration predominantly composed of lymphocytes with occasional neutrophils seen both within and around vessels (see Fig. 2). The findings were highly suggestive of urticarial vasculitis.

Prior to discharge, she was clinically asymptomatic and her inflammatory markers continued to improve.

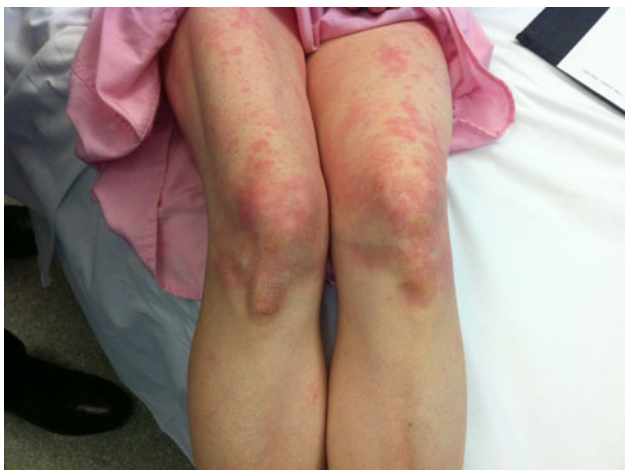

Fig. 1 Initial presentation of erythematous, maculopapular pruritic rash on lower limbs

Mycoplasma pneumoniae antibody titre returned as a positive result with a fourfold increased titre between paired acute sera (1:40) and convalescent sera (1:160) 10 days apart. At follow-up 1 week after discharge, she remained well with a white cell count 8 × 10^9/l, C-reactive protein 38 mg/l, erythrocyte sedimentation ratio 39 mm/h, alkaline phosphatase 139 iu/l and alanine transaminase 39 iu/l, normal C3 and C4, and ferritin of 1,231 g/l.

Discussion

Mycoplasma pneumonia is endemic worldwide, with epidemic peaks every 4–7 years, and typically affects women between 30 and 39 years of age and men between 3 and 19 years of age [3].

The infection has a 2–3-week incubation period and typically presents with an insidious onset of fever, cough and malaise. It accounts for up to 40% of community-acquired pneumonia, and in up to 25% of cases, a wide variety of extrapulmonary manifestations may occur, sometimes without clinical pneumonia (see Table 2) [4]. Up to a third of patients with *M. pneumonia* infections have cutaneous manifestations. Various types of urticaria are present in up to 7% of *M. pneumonia* infections, including generalised urticaria and cold urticaria [5]. However, only one other case report describes urticarial vasculitis (UV), confirmed on histology, occurring in a 51-year-old female with *M. pneumonia* who also had lower lobe pneumonia and episcleritis. She responded well to antibiotic therapy [2].

Mycoplasma pneumonia may be detected by serological testing, which requires several days; hence, it may be overlooked. A positive test is the detection of a fourfold increased titre in IgM, detected a minimum of 7–10 days after infection, or IgG, detected a minimum of 3 weeks after infection, between paired acute and convalescent sera. This is considered the gold standard. As *M. pneumoniae* is a fastidious organism, culture is time-consuming and expensive. A newer and faster technique is by polymerase chain reaction (PCR), which can detect *M. pneumonia* DNA. The latter has 78–92% sensitivity and 92–100% specificity [6].

Macrolides are the antibiotics of choice for treating *M. pneumonia* respiratory tract infections in both adults and children. The pathogenesis of extrapulmonary disease is not fully known, but it is thought to be secondary to either post-inflammatory response or direct tissue damage by the infective agent. Hence, management of extrapulmonary complications remains controversial. Supportive management is thought to be the most important management step although steroids, plasmapheresis and plasma exchange have been used to treat patients with severe neurological complications [4].

Table 1 Yamaguchi criteria for the diagnosis of adult-onset Still's disease (Presence of at least 5 criteria, of which at least 2 are major criteria, is required for diagnosis) [11]

Yamaguchi criteria	
Major	Minor
Temperature of >39°C for >1 week	Sore throat
Leukocytosis >10,000/mm^3 with >80% PMNs	Lymph node enlargement
Typical rash	Splenomegaly
Arthralgias >2 week	Liver dysfunction (high AST/ALT)
	Negative ANA, RF
Exclusion criteria	
Infection, sepsis	
Malignancy	
Inflammatory disease	

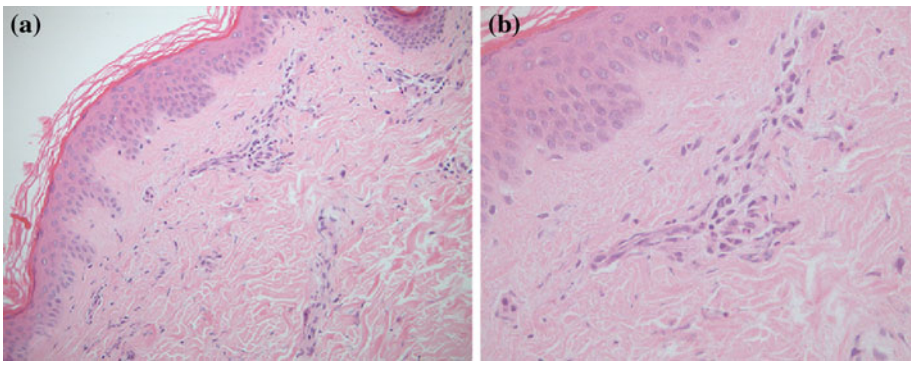

Fig. 2 Superficial perivascular inflammatory infiltrate predominantly composed of lymphocytes and neutrophils suggestive of UV (haematoxylin and eosin; **a** original magnification ×100, **b** original magnification ×400)

Table 2 Systemic manifestations of *M. pneumonia* infection

Respiratory	Skin	Rheumatological	Neurological
Pharyngitis	Exanthematous skin eruptions 8–33% of all *M. pneumoniae* cases	Myalgias	Encephalitis
Bronchitis	Erythema nodosum (8%)	Arthralgias	Meningoencephalitis
Pneumonia	Urticaria	Polyarthritis	Polyradiculitis
Pleural effusions	Steven's Johnson syndrome	Rhabdomyolysis	Meningitis
Acute respiratory distress syndrome			Transverse myelitis
Asthma			Guillain–Barré syndrome

Haematology	Gastrointestinal	Renal	Cardiac
Haemolytic anaemia	Hepatitis	Glomerulonephritis	Pericarditis
Cold agglutinin formation	Diarrhoea	Renal failure	Myocarditis
Aplastic anaemia	Pancreatitis	Tubulointerstitial nephritis	Pericardial effusion
Diffuse intravascular coagulation		IgA neuropathy	

Adult-onset Stills' disease (AOSD) is a rare disease presenting in young adults. Clinical features include fever, sore throat, arthralgia, a transient rash and lymphadenopathy. The rash characteristically coincides with febrile episodes and is salmon-pink, maculopapular, non-pruritic and predominantly present over the trunk and limbs.

The aetiology of AOSD remains unknown. Infections such as rubella, mumps, coxsackie, Epstein–Barr virus and parvovirus B19 have been associated with triggering AOSD. AOSD may represent a reactive process to certain infections, but it is widely thought that immune, genetic and environmental factors may also play a role [7].

To the best of our knowledge, only two case reports have previously reported *M. pneumonia* triggering AOSD [8, 9]. *M. pneumoniae* has also been implicated in causing juvenile idiopathic arthritis (JIA) [10].

AOSD is a clinical diagnosis of exclusion, and Yamaguchi's diagnostic criteria (see Table 1) [11] are commonly used as they have a sensitivity of 96% and specificity of 92%. Raised serum ferritin levels have

diagnostic value in acute AOSD, although it can be raised in other conditions such as severe sepsis, malignancy and liver disease [12].

AOSD may follow three different patterns: a monophasic self-limiting course, a polycyclic intermittent course; or a chronic severe articular pattern. Non-steroidal anti-inflammatory drugs (NSAIDS) and corticosteroids are first-line drugs used in the management of AOSD. In steroid refractory cases, disease-modifying antirheumatic drugs including methotrexate, azathioprine and IL-1 antagonists such as anakinra may also be used.

This patient had symptoms that are characteristic of both *M. pneumoniae* and AOSD, such as fever, pharyngitis, arthralgia, hepatitis and leucocytosis. She fulfilled the Yamaguchi criteria and had a raised ferritin level >3,000 g/l, and her symptoms resolved after commencing an NSAID, in support of AOSD. However, in effect, only 7–15% of AOSD patients respond to NSAIDS alone, hyperferritinaemia may have resulted secondary to sepsis, the rash was not a typical evanescent rash of AOSD, and *M. pneumoniae*-associated extrapulmonary symptoms are self-limiting and best managed with supportive treatment. In addition, the presence of any infection precludes the diagnosis of AOSD.

The skin biopsy specimen in this case was highly suggestive of urticarial vasculitis (UV), which is a rare clinicopathologic diagnosis, consisting of the clinical manifestation of urticaria with the histopathological demonstration of cutaneous leukocytoclastic vasculitis (LCV) of the small vessels. UV is categorised into hypocomplementemic and normocomplementemic subtypes. Patients with hypocomplementemia have associations with systemic conditions more frequently than normocomplementaemic types, as demonstrated in this case.

Although UV is a very rare manifestation of *M. pneumoniae*, clinicians should be alerted to consider this differential in cases of fever with urticaria that lasts longer than 24 h, is of a burning character and resolves with a degree of residual pigmentation [1].

Cutaneous LCV without urticaria can also occur secondary to *M. pneumoniae*, possibly secondary to an immune-mediated reaction triggered by *M. pneumoniae* antigens [13, 14].

Urticaria without vasculitis has also been reported to occur infrequently in AOSD [15, 16] and JIA [17]. However, UV is not known to be associated with AOSD.

This case highlights the importance of maintaining a high index of suspicion for diagnosing *M. pneumonia* in the context of pyrexia of unknown origin as its serological diagnosis may take a few weeks and it may therefore be missed. In addition, it is easily treatable and usually remains a monophasic illness, unlike chronic rheumatic conditions.

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