

Immune Thrombocytopenia Associated with *Mycoplasma pneumoniae* Infection

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ABSTRACT

Immune thrombocytopenia (ITP) related to *Mycoplasma pneumoniae* infection is a rare condition and usually associated with a severe clinical course. We here report a case of a young man with a clinical diagnosis of severe ITP secondary to *M. pneumoniae* infection. The clinical features, therapy and outcome are presented.

LEARNING POINTS

- Immune thrombocytopenia (ITP) related to *Mycoplasma pneumoniae* infection is a rare condition.
- ITP secondary to *M. pneumoniae* infection appears to be associated with a more severe and refractory clinical course.
- It remains unclear whether specific anti-*Mycoplasma* antibiotic therapy is associated with a milder clinical course and a better prognosis.

KEYWORDS

Immune thrombocytopenia, *Mycoplasma pneumoniae*, rituximab

INTRODUCTION

Immune thrombocytopenia (ITP) is one of the more common causes of thrombocytopenia in otherwise healthy adults. Thrombocytopenia associated with *M. pneumoniae* infection is a rare condition which usually has a severe course. We report the case of a young man with a clinical diagnosis of severe ITP that was associated with *M. pneumoniae* infection. Extra-pulmonary features of *M. pneumoniae* infection occur in 20–25% of cases, with the most commonly associated haematological abnormality being haemolytic anaemia due to the formation of cold agglutinin antibodies against erythrocyte I antigen^[1]. Thrombocytopenia associated with *M. pneumoniae* is usually associated with thrombotic thrombocytopenic purpura or disseminated intravascular coagulation, but association with ITP is rare.

CASE DESCRIPTION

A 24-year-old male college student was admitted to the emergency department with a 1-day history of reddish lesions on both legs (*Fig. 1*), a tongue haematoma following accidental bite (*Fig. 2*) and two small back bruises, self-induced after pinching himself. He remembered having odynophagia and serous rhinorrhoea without a cough or fever 2 weeks before admission. With a history of infectious mononucleosis at the age of 16, he had had recurrent tonsillitis ever since. He was physically very active and his medication history included protein supplements and a one-time-only use of sildenafil.



Figure 1. Reddish lesions on both legs suggestive of petechiae and purpura of the inferior limbs

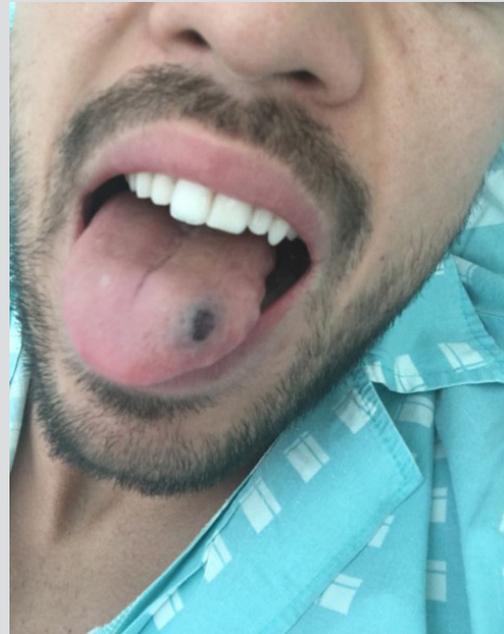


Figure 2. Tongue haematoma

Initial evaluation revealed normal vital signs, with a body temperature of 36.7°C, blood pressure of 132/61 mmHg, pulse rate of 54 beats/min and O₂ saturation of 100% on room air. He had petechial and purpuric lesions on both legs, slightly palpable hepatosplenomegaly and no identifiable adenopathies. The remaining physical examination was normal.

Complete blood count showed haemoglobin of 14.6 g/dl, leucocyte count of 5.7×10^9 cells/l and platelet count of 3×10^9 cells/l. Coagulation, liver and renal studies were normal. CRP was 1.15 mg/dl. A peripheral blood smear confirmed severe thrombocytopenia without abnormal cells. A chest x-ray did not show any signs of pleuroparenchymal lung disease and abdominal ultrasound confirmed the presence of moderate homogeneous hepatosplenomegaly.

A presumptive diagnosis of ITP was made, corticoid treatment was promptly initiated and the patient was hospitalized. No platelet count response was seen following a 3-day course of methylprednisolone 1 g IV. Oral prednisolone 1 mg/kg/day and a 3-day course of intravenous immunoglobulin (IVIG) 1 g/kg was therefore initiated with an increase in platelet count to 48×10^9 cells/l the day after. However, on the very next day, the platelet count dropped once again to 2×10^9 cells/l. A second 3-day course of methylprednisolone 1 g IV in association with 4 more days of IVIG 1 g/kg was given with no platelet response. The patient remained clinically stable until the 11th day of hospitalization when he presented with epistaxis (Fig. 3), gingival haemorrhage, vascular puncture site haematoma (Fig. 4) and new petechiae on the face and trunk. Prednisolone dosage was increased to 1.5 mg/kg/day and the anti-CD20 monoclonal antibody rituximab 375 mg/m² IV was also initiated. Bone marrow examination revealed normal cellularity with megakaryocytic hyperplasia but no cell abnormalities, compatible with the diagnosis of ITP. A thoraco-abdomino-pelvic CT scan did not show any lymphadenopathies or lesions suggestive of a neoplastic process. Serological testing for EBV, CMV, HCV, HBV, HIV, HSV and parvovirus B19 was negative for acute infection. A urea breath test for *Helicobacter pylori* was negative. Assays for ANA, dsDNA, rheumatoid factor, anticardiolipin, lupus anticoagulant and anti-beta-2 glycoprotein were also negative. Antiplatelet antibodies were positive and a positive *M. pneumoniae* IgM titre was found. ITP secondary to *M. pneumoniae* infection was assumed, and clarithromycin 500 mg twice a day was added to the treatment regimen.

By the 14th day of hospitalization the platelet count was still 4×10^9 cells/l and the patient presented with gross haematuria. As a consequence, two pools of platelets were given and he was transferred to the intermediate care unit for closer observation. He became hypertensive (blood pressure of 170/90 mmHg), anaemic (with haemoglobin dropping to 8.9 g/dl) and developed a constant headache and occasional haemolacria (Fig. 5). A cranial CT scan excluded any haemorrhagic lesions.

Six days after the second dose of rituximab (on the 24th day of hospitalization), the platelet count slowly started to rise to 21×10^9 cells/l.



Figure 3. Epistaxis



Figure 4. Vascular puncture site haematoma



Figure 5. Haemolacria

Given the subsequent resolution of haematuria and other haemorrhagic dyscrasia, the dose of oral prednisolone was reduced to 1 mg/kg/day and the patient was transferred back to the medicine ward, where he completed treatment with rituximab.

From the 25th day of hospitalization onwards, the platelet count gradually increased, as did haemoglobin values. The patient was discharged on the 28th day after admission with a platelet count of 229×10^9 cells/l and no signs of blood dyscrasia. He returned for 2-week follow-up asymptomatic and with a platelet count of 273×10^9 cells/l, slowly tapering oral prednisolone as advised upon discharge.

DISCUSSION

Haematological abnormalities associated with *Mycoplasma* infection are widely described, but association with ITP is rarely reported^[2]. We identified 10 similar case reports in a literature research. Table 1 summarizes the clinical features and outcomes of those cases. Most patients (7 out of 10) were male and the mean age was 18 years (ranging from 7 months to 64 years). The most common clinical presentation was respiratory infection (cough, fever and dyspnoea) and mild haemorrhagic manifestations (petechiae, purpura and epistaxis). Two patients presented with more severe forms of haemorrhage (haemoptysis, haematuria and haematochezia), while three patients did not have any haemorrhagic symptoms at all. The mean platelet count on admission was 11×10^3 cells/l. Apart from one patient, all subjects underwent corticosteroid therapy. In three of them IGIV therapy was given as well. Empiric antimicrobial therapy was administered to eight patients, targeting atypical bacteria, in most cases through macrolide usage. Interestingly, none of the patients required rituximab. The mean time required for platelets to rise above 150×10^3 cells/l was 21 days. In most cases evidence for *Mycoplasma* infection came from a complement fixation test, cold agglutinin test or IgM titre. Two patients experienced intracranial haemorrhage and died. Although incompletely understood, the pathogenesis of ITP is thought to involve the formation of specific autoantibodies against platelet cell membrane glycoproteins, more commonly GPIIb/IIIa^[3].

In up to 60% of patients, *M. pneumoniae* infection manifests itself only by odynophagia and rhinorrhoea, as in our patient.

Several physiopathological mechanisms have been described to explain the production of antiplatelet antibodies following *Mycoplasma* infection, such as molecular mimicry, the development of immune complexes that may cause platelet aggregation, serotonin release, and clearance of platelets^[4] and even direct binding of *Mycoplasma* to the platelets, generating a complex that is then recognized as foreign by the immune system.

Secondary ITP associated with *M. pneumoniae* infection appears to have a more severe clinical course and, to some extent, to be a refractory disease, as evidenced by the referenced cases and our own.

About 66% of patients with ITP respond to steroid therapy after 1–2 weeks. Our patient was found to be corticosteroid resistant which first led to the need to initiate IGIV therapy and later, given the poor clinical response, to second-line therapy with rituximab.

Rituximab is a monoclonal antibody directed against the B cell surface protein CD20. Response to this therapy can occur within a week but may take up to 2 months. In this case our patient had a partial response on day 14 and a complete response after 15 days of rituximab therapy.

Specific anti-*Mycoplasma* therapy was initiated but, in our case, had no apparent effect on the clinical course or outcome, so given the very few cases described, we cannot evaluate the benefit of this particular therapy.

CONCLUSION

Considering the clinical features described above, ITP secondary to *M. pneumoniae* infection appears to be associated with a more severe and refractory clinical course. It remains unclear whether specific anti-*Mycoplasma* antibiotic therapy is associated with a milder clinical course and a better prognosis.

Case	Age (yrs) Sex	Clinical Presentation	Platelets on admission ($\times 10^3$ cells/l)	<i>Mycoplasma</i> testing	Complications	Treatment	Time to platelets >150 ($\times 10^3$ cells/l)
Current case	24, Male	Petechiae and purpura, odynophagia and serous rhinorrhoea 2 weeks previously	3	IgM 29.9	Epistaxis, gingival haemorrhage, haematuria, haemolacria, anaemia and headache	Methylprednisolone, IVIG, prednisolone, rituximab, clarithromycin	28 days
Tsai et al. ^[5]	0,7, Female	Cough, fever, dyspnoea (pneumonia) and petechiae	14	Complement fixation test 1:4; cold agglutinin 1:128	None	Prednisolone, minocycline	14 days
Miller et al. ^[6]	44, Male	Cough, fever (pneumonia), haematuria	7	Complement fixation test 1:4 to 1:32; cold agglutinin 1:128	Brain stem haemorrhage, death on day 14	Erythromycin, cefotaxime, amikacin, methylprednisolone	Never
Veenhoven et al. ^[7]	17, Male	Cough, fever, dyspnoea (pneumonia) and petechiae	25	Complement fixation test 1:64; IgM+cold agglutinin 32-256	None	Prednisolone, erythromycin	3 months
Beattie ^[8]	4, Male	Cough, fever (pneumonia)	4	IgM 80-320	Purpura, epistaxis and haematuria	IGIV	Not mentioned, 42×10^3 cells/l on day 5
Pugliese et al. ^[9]	7, Male	Sinusitis, fever	<18	ELISA 1.01; cold agglutinin 1:64	Headache, vomiting, diarrhoea	Ceftriaxone, erythromycin, prednisone	14 days
Isoyama et al. ^[10]	8, Male	Rhinorrhoea, cough, epistaxis, petechiae and haematoma of the skin	2	ELISA 4 to >1.5; 3 positive cultures	Epistaxis, haematuria and haematochezia	Prednisone, IVIG	14 days
Venkatesan et al. ^[11]	21, Male	Cough, fever (pneumonia), purpura, haemoptysis, haematuria and haematochezia	6	Complement fixation test 1:8000; total anti-mycoplasma 1:5120	Intracranial haemorrhage; death on day 2	Cefotaxime, methylprednisolone, erythromycin	Never
Scimeca and James-Herry ^[12]	7, Male	Otitis media, fever	5	<i>Mycoplasma pneumoniae</i> titre and antibody	Petechiae	Amoxicillin, erythromycin, prednisone	1 week
Okoli et al. ^[13]	64, Female	Cough, dyspnoea, epistaxis, purpura and bruising	3	IgM+cold agglutinin	None	Moxifloxacin, dexamethasone 40 mg	3 months
Aviner et al. ^[14]	7, Female	Cough, fever (pneumonia), petechiae and purpura	2	IgM+total anti-mycoplasma 1:64	Haemoptysis	IVIG, prednisolone, clarithromycin	2 months

Table 1. Clinical features and outcomes of *Mycoplasma* infection-associated immune thrombocytopenia

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