CASE REPORT

Transient immune-mediated agranulocytosis following *Mycoplasma pneumoniae* infection

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SUMMARY

Mycoplasma pneumoniae is a common respiratory pathogen which may cause haematological manifestations including haemolytic anaemia and thrombocytopaenia. Severe neutropaenia is rare with very few cases reported in the literature. An 85-year-old man was transferred to our facility with agranulocytosis in the context of an infective exacerbation of chronic obstructive pulmonary disease with positive serological testing for *M. pneumoniae*. No alternative infective, autoimmune or lymphoproliferative cause of the neutropaenia was identified. Granulocyte autoantibody testing was performed with a positive result for neutrophil-bound IgG and IgM autoantibodies and significant agglutination reactions. The patient was treated with azithromycin and granulocyte colony-stimulating factor which resulted in a sustained resolution of his neutropaenia.

BACKGROUND

Mycoplasma pneumoniae is a common cause of community-acquired pneumonia, mainly affecting children and young adults although it is not uncommon in the adult population.¹ Numerous extrapulmonary manifestations have been reported. Immunohaematological abnormalities described include cold agglutinin haemolytic anaemia, aplastic anaemia and immune thrombocytopaenia.^{2–3} In contrast, neutropaenia associated with *M. pneumoniae* infection in adults appears to be rare with only two published case reports.^{4,5}

Neutropaenia less than $1.5 \times 10^9/L$ that is associated with normal granulopoiesis on bone marrow examination is often presumed to be immune-mediated. The presence of antigranulocyte antibodies in patient plasma strongly supports this mechanism. Typical causes include systemic autoimmune diseases, haematological and non-haematological malignancy, infectious diseases such as human herpes virus 8, HIV and drugs.⁶ Conversely, agranulocytosis (defined as severe neutropaenia with absent or minimal granulopoiesis on bone marrow examination) is most commonly seen as an idiosyncratic drug reaction, with rarer cases described in patients with thymoma.⁷

Here, we report a case of confirmed agranulocytosis in an elderly patient with recent *Mycoplasma* infection and detectable antigranulocyte antibodies, which resolved with antibiotic therapy and granulocyte colony-stimulating factor (G-CSF) treatment.

CASE PRESENTATION

An 85-year-old man was transferred to our facility, a tertiary Australian hospital, after being treated for 1 week at a peripheral hospital for an infective exacerbation of chronic obstructive pulmonary disease (COPD). He presented with a 2-week history of subjective fevers and cough and was managed with ceftriaxone and bronchodilator therapy at the peripheral hospital. Laboratory testing on initial admission to hospital showed moderate neutropaenia which worsened during the course of his treatment, prompting transfer to our unit for specialist Haematology opinion.

The patient's medical history was significant for ischaemic heart disease, gout, stage III chronic kidney disease, COPD and stage I lung adenocarcinoma resected 12 years prior with no evidence of recurrence on regular follow-up. He had an allergy to penicillin manifesting as a rash. His regular medications included allopurinol 500 mg daily and colchicine 0.5 mg two times per day for gout. There had been no recent changes to his medications prior to presentation. Blood tests performed 5 months prior to his presentation included a normal full blood count.

On examination at admission to our facility, the patient was haemodynamically stable, afebrile and had a 2 L/min oxygen requirement. Respiratory examination revealed crackles in the right lower zone with bilateral rhonchi. He had no other abnormal findings on examination including no palpable lymphadenopathy or hepatosplenomegaly.

INVESTIGATIONS

Initial investigations showed a mild anaemia and thrombocytopaenia, with neutropaenia of $0.8 \times 10^9/L$ (see table 1). There was a mild rise in the serum creatinine to 161 mmol/L from a baseline of 130 mmol/L, equating to a calculated creatinine clearance of 33 mL/min from a baseline of 40 mL/min.⁸ Liver function tests were unremarkable.

The blood film showed red cell agglutination and neutropaenia with normal cytomorphology. The direct antiglobulin test was reactive for C3d but serum haptoglobin, lactate dehydrogenase and reticulocyte count were normal.

Chest X-ray revealed right lower and mid-zone opacification. CT of the chest, abdomen and pelvis showed emphysematous changes with ground glass opacification in the right lower lobe and low-volume mediastinal and hilar lymphadenopathy. There was no hepatosplenomegaly or evidence of metastatic

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Table 1 Full blood count results during the patient's hospitalisation

Day	1	10	15	20	22
Haemoglobin (g/L)	120	105	106	110	118
Leucocyte count ($\times 10^9/L$)	2.4	0.9	1.3	2.3	5.0
Platelet count ($\times 10^9/L$)	126	176	230	239	212
Neutrophil count ($\times 10^9/L$)	0.8	0.00	0.00	0.02	1.93
Lymphocyte count ($\times 10^9/L$)	1.0	0.68	1.01	1.53	1.63

malignancy. Sputum microscopy culture and sensitivity grew normal respiratory flora only, and nasopharyngeal swab polymerase chain reaction for common respiratory viruses was negative. Blood cultures were also negative. Serological testing for *M. pneumoniae* was positive with a titre of 1:160 on two separate occasions.

The patient developed absolute neutropaenia by day 10 of his admission (figure 1). Testing for secondary causes including HIV, hepatitis B and C, parvovirus B19, cytomegalovirus and Epstein-Barr virus was negative. Antinuclear antibodies were not detected and B12 and folate levels were normal.

Peripheral blood flow cytometry was normal. Serum electrophoresis revealed a trace kappa IgM paraprotein with a normal light chain ratio. Bone marrow aspirate showed a normocellular marrow with marked reduction in granulopoiesis involving all stages of maturation. Megakaryopoiesis was normal and erythropoiesis was relatively increased with normal nest formation. No abnormal lymphoid infiltrate was identified.

Blood collected on day 14 of his admission was tested for granulocyte autoantibodies due to this unusual presentation. The granulocyte immunofluorescence test (GIFT) returned a positive result for neutrophil-bound IgG and IgM autoantibodies. Further GIFT screening of his adsorbed serum against a typed neutrophil panel identified IgM antibodies without antigen specificity. The granulocyte agglutination test of his adsorbed serum showed significant agglutination reactions against all the panel cells.

DIFFERENTIAL DIAGNOSIS

The laboratory testing supported a diagnosis of immune-mediated agranulocytosis. Possible causes included medication

exposure leading to formation of drug-dependent antibodies, infection with atypical or viral organisms, lymphoproliferative disease, autoimmune conditions such as Sjogren's syndrome, thymoma and aplastic anaemia.

TREATMENT

Following admission to our facility, the patient was commenced on treatment with azithromycin and continued on broad-spectrum therapy with cefepime for febrile neutropaenia. G-CSF was commenced following bone marrow aspirate until recovery of neutrophil count (see figure 1).

OUTCOME AND FOLLOW-UP

Twenty days following his initial presentation, the patient's neutrophil count rapidly recovered to $1.93 \times 10^9/L$ (figure 1). At this time, the patient was well and was discharged home the following day.

At routine review 3 months post-discharge, the patient's neutrophil count was $3.55 \times 10^9/L$ with a normal blood film. The trace paraprotein noted on earlier serum electrophoresis was no longer detectable. Repeat CT chest showed resolution of the right lower lobe consolidation and mediastinal lymphadenopathy. Antigranulocyte antibodies were no longer detectable on follow-up testing 18 months later.

At the time of writing, it was noted that the patient had been restarted on colchicine but allopurinol has not been reinitiated.

DISCUSSION

Mycoplasma pneumoniae is known to cause multiple extrapulmonary manifestations which may present a diagnostic and therapeutic challenge. In this case report, we have presented a rare case of agranulocytosis in the setting of serologically confirmed *M. pneumoniae* infection with transient antigranulocyte antibodies, suggesting a para-infective immune mechanism analogous to other immune cytopenias described with this organism. In our case, anaemia and thrombocytopenia were present but disproportionately mild in comparison to the neutropaenia. Postulated mechanisms of these haematological manifestations include antibody cross-reaction with erythrocyte I antigen in the

Figure 1 Absolute neutrophil count during hospitalisation. G-CSF, granulocyte colony-stimulating factor.

case of cold agglutinin haemolytic anaemia.⁹ Cases of thrombocytopenia with *M. pneumoniae* infection have also been reported with antiplatelet antibodies.²

In our case, antigranulocyte antibodies were detected during the acute presentation and had resolved on review 18 months later. The transient detection of antigranulocyte antibodies supports an immune mechanism of agranulocytosis in this case.

One previous case of an adult with isolated neutropaenia associated with *M. pneumoniae* has been reported in a patient presenting febrile neutropaenia.⁴ In the case reported by Celik *et al*, bone marrow aspirate showed hypergranulation of myeloid precursors with a paucity of myeloid maturation. An immune mechanism was hypothesised; however, antigranulocyte antibodies were not tested. The possibility of an immune mechanism is also supported by the finding of antigranulocyte antibodies in a 4-year-old child with neutropaenia and thrombocytopenia in the context of *M. pneumoniae* infection.⁵

We cannot entirely exclude the possibility of drug-induced agranulocytosis secondary to colchicine or allopurinol. Typically, colchicine-associated myelosuppression has been reported in overdose; however, there have been reports of neutropaenia in patients taking non-toxic doses in the context of end-stage renal failure, recent dose changes or initiation of interacting medications.^{10–12} In this case, the patient's colchicine dose was unchanged from previous, his renal function was only mildly reduced from baseline and the cardinal colchicine toxicity symptom of diarrhoea was absent. Rare cases of neutropaenia associated with allopurinol have also been reported,¹³ but in our experience, this is extremely uncommon in patients on long-term stable doses of this drug. Ceftriaxone has been associated

with agranulocytosis in three prior case reports; however, the patient in this case had significant neutropaenia on initial presentation prior to the administration of ceftriaxone.¹⁴

To our knowledge, this is the first report of agranulocytosis with transient positive antigranulocyte antibodies in an adult with *M. pneumoniae* infection. These findings may aid our understanding of the pathogenesis of the indirect effects of *M. pneumoniae* infection and add to the awareness among clinicians of the various fascinating haematological manifestations of this disease.

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Learning points

- *Mycoplasma pneumoniae* is a common cause of community-acquired pneumonia which is often considered in the differential diagnosis of cold antibody haemolysis.
- Agranulocytosis is a rare condition that may arise from formation of antigranulocyte antibodies generated by the immune response to Mycoplasma infection
- The differential diagnosis for new-onset neutropaenia include medication side effects, viral infection and lymphoproliferative disorders; acute Mycoplasma infection should also be considered.
- This case of Mycoplasma-associated agranulocytosis responded well to appropriate antibiotic treatment and growth factor support.

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