Macroscopic haemoglobinuria associated with Mycoplasma pneumoniae infection successfully treated by clarithromycin

Emoglobulinuria macroscopica secondaria a infezione da Mycoplasma pneumoniae trattata con successo con claritromicina

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INTRODUCTION

Mycoplasma pneumoniae infections are usually characterized by upper or lower respiratory symptoms, including sore throat, hoarseness, rhinorrhea, fever and prolonged coughing [1]. Although these symptoms are often self-limiting, 3 to 10% of the patients develop clinical pneumonia [2]. However, since such respiratory symptoms are primarily induced by the direct toxicity of the organisms, they respond well to anti-microbial treatment [3].

On the other hand, as many as 25% of the patients with M. pneumoniae infection develop extra-pulmonary manifestations, which include haemolysis, skin rash, joint involvement and symptoms or signs involving the gastrointestinal tract, central nervous and cardiovascular systems [4]. These manifestations often occur weeks after the onset of the primary infection and sometimes persist in the absence of the respiratory symptoms, suggesting the involvement of immunological factors in the pathogenesis [5].

Recently, we reported two cases of M. pneumoniae infection complicated with exacerbated atopic dermatitis [6]. In these cases, due to the lymphocyte-stimulatory nature of the microorganisms, increased immunological responses were likely to have been involved in the pathogenesis of the skin manifestation [7]. “Cold agglutinins” are the IgM antibodies frequently produced in patients with M. pneumoniae infection as a result of the enhanced humoral immunity [8]. These autoantibodies can cause erythrocyte haemolysis, leading to autoimmune haemolytic anaemia or haemoglobinuria [9].

For the treatment of haemolytic anaemia secondary to M. pneumoniae infection, previous case reports demonstrated the usefulness of warming, glucocorticoid administration, or possibly plasmapheresis [10]. However, a recent case report also suggested the therapeutic efficacy of antibiotics alone for resolution of the haemolysis [11]. Here, we experienced a case with M. pneumoniae infection complicated with macroscopic haemoglobinuria, for which the usefulness of clarithromycin was demonstrated. In this case, an enhanced immune response, such as the production of cold agglutinins, was likely involved in the pathogenesis of erythrocyte haemolysis.

The immunomodulatory property of clarithromycin was thought to have repressed the increased immunological reaction and thus enabled the resolution of the urine abnormality.
A 25-year-old man with an unremarkable past medical history came to our outpatient clinic because of a persistent dry cough for the previous 2 weeks. Three days prior to his visit, he presented with a dark red-colored urine, which was later revealed to be macroscopic haemoglobinuria (Figure 1).

On physical examination, the patient looked tired. His body temperature was 36.4°C, blood pressure was 110/70 mmHg, and pulse rate was 72 beats/min. He weighed 52 kg and was 170 cm tall. Although there was no sign of anaemia in the eyes, he apparently showed scleral icterus. His oral mucosa was moist and the pharynx was slightly reddish.

On examination of the neck, cervical lymph nodes or masses were not palpable. No crackles, wheezes or stridors were heard on lung auscultation. Laboratory data showed an increased peripheral white blood cell count (11,800/μl) and an elevated C-reactive protein level (3.64 mg/dl). Since the IgM antibody specific to Mycoplasma pneumoniae, determined by particle agglutination, was high (1:320) with a significant rise in the IgG titer, a recent infection with the organism was likely. However, since a chest radiograph revealed no signs of pulmonary infiltrates, acute bronchitis caused by M. pneumoniae was likely responsible for the prolonged coughing.

Although haematological parameters, including red blood cell count (5,110,000/μl), haemoglobin concentration (14.6 g/dl) and haematocrit value (41.9 %), were normal, the marked increase in haemolytic markers, such as serum lactate dehydrogenase (LDH; 998 IU/l) and total bilirubin (3.3 mg/dl) levels, indicated the haemolysis of red blood cells. Additionally, since urine haemoglobin was positive despite the absence of red blood cells in the urine sediment, the initially observed dark red-colored urine was likely gross haemoglobinuria as a result of erythrocyte haemolysis. Shortly after the initiation of clarithromycin (400 mg/day) for the M. pneumoniae infection, his persistent dry cough had completely resolved, together with the complete disappearance of haemoglobinuria and gradual improvement of haemolytic markers (Figure 1). Clarithromycin was continued for 14 days, and no recurrence of the symptoms or signs was noted afterwards, indicating complete remission of the disease.

In the present case, since the patient developed gross haemoglobinuria secondary to the onset of
Mycoplasma infection, and since it completely disappeared with the resolution of the disease (Figure 1), the symptom was likely to have been triggered by infection with an organism. In response to \textit{M. pneumoniae} infection, autoantibodies called “cold agglutinins” are frequently produced, which cause erythrocyte haemolysis in about 10\% of such patients [12]. In our case, we failed to perform a direct Coombs test to detect the antibodies, nor did we directly examine the titers of cold agglutinins.

However, since other causes that trigger erythrocyte haemolysis, such as an infection with a causative virus, the use of anti-inflammatory or antimicrobial drugs, and the prevalence of inherited haemolytic diseases, were absent, infection with \textit{M. pneumoniae} was most likely to be responsible for the urinary abnormality [13, 14].

Mycoplasmas are known to stimulate the activity and cytokine production of lymphocytes, and the symptoms caused by such organisms are believed to be immune-mediated rather than induced directly by their cellular toxicity [7, 10]. Additionally, other than the cold agglutinins, a variety of cross-reactive antibodies or circulating immune complexes are produced in association with \textit{M. pneumoniae} infection [15].

Therefore, the infection has often been associated with the subsequent onset of immune-mediated systemic disorders, such as autoimmune haemolytic anaemia, Stevens-Johnson syndrome, thrombocytopenic purpura and organizing pneumonia [16-19].

Previously, we experienced cases of \textit{M. pneumoniae} infection co-infected with \textit{Bordetella pertussis} or \textit{Chlamyphila pneumoniae} [6, 20]. In these patients, the organisms exerted multipliable effects in enhancing the cellular immunity, causing an exacerbation of atopic dermatitis [6] or the migration of pulmonary infiltrates [6, 20].

In the present case, since the patient’s haemoglobinuria disappeared shortly after the initiation of clarithromycin (Figure 1), the drug was thought to be responsible for the resolution of the symptom. In addition to its broad-spectrum antimicrobial properties, macrolide antibiotics exert immunomodulatory effects by reducing the proinflammatory cytokine production from lymphocytes [21]. In our case, since an increased immunological reaction was involved in the pathogenesis of erythrocyte haemolysis, the immunomodulation by clarithromycin was thought to be the mechanism responsible for the resolution of the haemoglobinuria. Recently, we have demonstrated in a basic study that clarithromycin inhibits delayed rectifier K⁺-channels (Kv1.3) in lymphocytes, and thus exerts immunomodulatory effects [22]. In our series of experiments, we further demonstrated that drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), dihydropyridine Ca²⁺-channel blockers (DHP CCBs) and HMG-CoA reductase inhibitors (statins), also effectively suppressed the channel currents [23-25].

Therefore, in this regard, besides the use of corticosteroids, the use of these Kv1.3-channel inhibitors may also be useful for the resolution of haemoglobinuria complicated with \textit{M. pneumoniae} infection [10].

In summary, this is the first report of a patient with \textit{M. pneumoniae} infection complicated with macroscopic haemoglobinuria, for which the usefulness of clarithromycin was demonstrated. The immunomodulatory property of clarithromycin was thought to repress the increased immunological reaction and thus enabled the resolution of erythrocyte haemolysis.

\section*{Declaration of interest}
The authors declare no conflicts of interest.

\section*{Authors’ contributions}
IK analyzed and interpreted the patients’ data. All authors approved the final manuscript.

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\section*{Keywords: Mycoplasma pneumoniae, macroscopic haemoglobinuria, increased immunological reaction, erythrocyte haemolysis, clarithromycin.}
A 25-year-old man developed macroscopic haemoglobinuria after a persistent dry cough. Although chest radiograph findings were normal, since the serum antibody for *Mycoplasma pneumoniae* was significantly elevated, a diagnosis infection with this organism was made. Despite the absence of apparent anaemia, a marked increase in serum haemolysis markers and positive result for urine haemoglobin indicated the haemolysis of red blood cells, which was likely to have occurred secondarily to *M. pneumoniae* infection. Shortly after the initiation of a macrolide antibiotic, clarithromycin, the patient’s haemoglobinuria completely disappeared together with a complete resolution of his respiratory symptoms. In this case, due to the lymphocyte-stimulatory nature of *M. pneumoniae*, an enhanced immune response, such as the production of cold agglutinins, was likely to be involved in the pathogenesis of erythrocyte haemolysis. The immunomodulatory property of clarithromycin was thought to repress the increased immunological reaction and thus enable the resolution of the urine abnormality.

**SUMMARY**

**REFERENCES**

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