Case report of mixed-type autoimmune hemolytic anemia in a patient with relapsing polychondritis

Qianyun Xu, MDab, Hui Luo, MDab, Xiaoxia Zuo, MDab, Sijia Liu, MDab,*

Abstract
Rationale: Relapsing polychondritis (RP) is a rare autoimmune-related disease and may be associated with other autoimmune diseases.

Patient concerns: Here we reported a case of RP patients with mixed-type AIHA. The patient was diagnosed with RP in March 2008 which was treated and the patient was in stable condition. Laboratory data revealed progressive decrease in hemoglobin during her hospitalization due to pulmonary infection in 2016. Positive Coombs’ test and moderate titer of anti-cold agglutinin was detected.

Diagnosis: Mixed-type AIHA was diagnosed as a comorbidity in this case given the circumstance that her RP was stable and low-dose oral corticosteroids was enough to maintain remission.

Interventions: The patient was treated with intravenous immunoglobulin and steroids.

Outcomes: The patient’s body temperature dropped and hemoglobin levels rose in 2 weeks.

Lessons: Reports of RP patients with autoimmune hemolytic anemia (AIHA) are extremely rare and cases with the mixed-type AIHA has not been reported. Here we describe a case of RP with mixed-type AIHA which was considered as a comorbidity rather than a complication.

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity, AIHA = autoimmune hemolytic anemia, ANCA = antigen presenting cell, C3 = complement 3, CT = computed tomography, DIIHA = drug-induced immune hemolytic anemia, HLA = human leukocyte antigen, IgG = immunoglobin G, MMP = metalloproteinase, RBC = red blood cell, Rh = rhesus, RP = relapsing polychondritis, SMZ = sulfamethoxazole, T6 = the sixth thoracic vertebra, T8 = the eighth thoracic vertebra, TNF = tumor necrosis factor.

Keywords: autoimmune hemolytic anemia, comorbidities, relapsing polychondritis

1. Introduction
Relapsing polychondritis (RP) is a rare relapsing-remitting destructive inflammatory disorder of the cartilaginous and other proteoglycan-rich structures. The frequent association with other rheumatologic and hematologic disorders has been extensively reported over time. In about 30% to 35% of cases, RP is associated with other autoimmune diseases such as antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides, rheumatoid arthritis, and Behcet disease.[1] However, reports of RP patients with AIHA are extremely rare, with only 3 cases reported in literature (see Table 1); cases with the mixed-type AIHA has not been reported. Herein we reported a case of mixed-type autoimmune hemolytic anemia (AIHA) in a patient with RP.

2. Case presentation
In March 2016, a 57-year-old woman was admitted to our hospital owing to polyarthralgia and bilateral auricular cartilage collapse since 8 years ago, fever and cough for 20 days. She was diagnosed with RP according to the Michet diagnostic criteria in March 2008 and treated with oral prednisone. She responded well to the drug and thus, the dose was reduced to 5mg/day, which kept her condition under control until her recent presentation.

Her past medical history included 2 previous occurrences of hemolytic anemia in September 2008 and July 2015, hypertension, cholelithiasis, and pulmonary nocardiosis. The last time hemolytic anemia recurred, she developed dark urine and low back pain without triggers. Current laboratory findings included anemia (hemoglobin 35g/L) and elevated bilirubin (total bilirubin 42.0 μmol/L and direct bilirubin 17.1 μmol/L). Both direct (anti-IgG and anti-C3) and indirect Coombs tests were positive and abdominal ultrasound revealed splenomegaly. Thus, the patient was diagnosed with hemolytic anemia, and intravenous dexamethasone was started at 20mg daily, followed by oral prednisone 45mg daily. Ciclosporin was administered at 100mg twice daily. The patient responded to the treatment, with hemoglobin levels increasing steadily to 148mg by 3-month follow-up. Laboratory data revealed elevated inflammation markers. Blood and sputum cultures were negative. Pulmonary computed tomography (CT) scan showed a high-density focus in the right lower lobe. Pulmonary infection was clinically diagnosed. The patient was empirically treated with several antibiotics but the fever did not resolve. Bacteriological examination of pulmonary biopsy yielded Nocardia nova. Consequently, sulfamethoxazole (SMZ) tablets were administered at 1.92g twice daily. However, the patient still had intermittent fever; thus, voriconazole (0.2 g...
twice daily) was added and symptoms improved. The patient was maintained on SMZ and voriconazole for *Nocardia* infection, methylprednisolone 12mg/day for RP, liver and stomach protection drugs, and calcium supplement drugs.

In September 2016, the patient was hospitalized for low back pain lasting half a month. The diagnosis of T6 to T8 (the sixth thoracic vertebra to the eighth thoracic vertebra) compression fracture was made after thoracic and lumbar spine CT scan; treatment involved calcium supplement and a trunk brace. Voriconazole was discontinued due to elevated liver enzymes and no exact evidence of fungal infection. SMZ was reduced to 1.44 g twice daily owing to digestive intolerance and weight loss. Three days later the patient had a fever. Pulmonary infection was considered after lung CT reexamination revealed high density areas bilaterally; 4 different antibiotics were empirically administered successively, but her body temperature was still abnormal. In the meantime, hemoglobin level reduced to 57 g/L with positive urobilinogen. Liver function tests revealed elevated direct bilirubin (13.1 μmol/L) and indirect bilirubin (16.7 μmol/L) levels. Both direct (anti-IgG and C3) and indirect Coombs' test results were positive. Moderate titer (1:128) of anticold agglutinin was detected. Given that hemolytic anemia happened 7 months after SMZ administration and dose was reduced, drug-induced immune hemolytic anemia (DIHA) was excluded and mixed-type AIHA was diagnosed. The patient was treated with a 6-day course of intravenous immunoglobulin, 40mg/kg per day. Intravenous methylprednisolone at 1 mg/kg daily was added. Consequently, the patient’s body temperature dropped and hemoglobin levels rose in 2 weeks. Subsequently, the steroids were gradually tapered.

This study was approved by the Ethics Committee of Xiangya Hospital of Central South University, Changsha, Hunan, China. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

### 3. Discussion

RP and AIHA are both rare autoimmune-related diseases. The prevalence of RP is 2 to 4.5 per million[5,6] and that of AIHA is 17 per million[5,6] while mixed-type accounts for 5% of cases.[8] AIHA can be primary or secondary. The most common secondary causes include systemic lupus erythematosus (64%), solid malignancies (13%), lymphomas (10%), drugs (8%), and infections (5%).[9] In this case, however, it is unclear whether AIHA was primary or secondary to RP.

Rabash et al[10] reported a case that the patient developed AIHA the same time at RP onset. Both AIHA and RP improved rapidly after prednisolone administration. The authors attributed AIHA to be hemoglobinolysis by immune complexes. However, in this case, it is unclear whether AIHA is caused by the increased destruction of red blood cells (RBCs) induced by anti-RBC autoantibodies with inadequate compensation. RBC destruction may occur by a direct lysis through the sequential activation of the final components of the complement cascade (membrane attack complex), or by anti-body-dependent cell-mediated cytotoxicity (ADCC). HLA-DQ6 has a negative correlation with the degree of hemolysis.[27] Rhesus (Rh) polypeptides are the most common targets for pathogenic autoantibodies in patients with warm AIHA, while in...
which are associated with a failure to control lymphoproliferation.

Addition, polyclonal activators such as superantigens or mitogens, presented by APCs.[28] Apart from antigen presenting failure, functional abnormalities of B and T cells may activate lymphocytes, produce cytokine, and thus induce autoimmunity.[23] In addition, polyclonal activators such as superantigens or mitogens, which are associated with a failure to control lymphoproliferation may explain autoaggressive damaging tissue responses.[22]

4. Conclusion

In the present study, we described a case of RP with mixed-type AIHA which was considered as a rare comorbidity rather than a complication. The present report adds an additional complication of RP, which may help further research into the pathogenesis of both diseases. For example, the way to escape immune tolerance may be a potential mechanism.

Author contributions

Methodology: Hui Luo.
Supervision: Xiaoxiao Zuo.
Writing – original draft: Qianyun Xu.
Writing – review & editing: Sijia Liu.

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