Clinical Case Report

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

Qianyun Xu, MD[a,b], Hui Luo, MD[a,b], Xiaoxia Zuo, MD[a,b], Sijia Liu, MD[a,b,*]

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, APC = 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[2–4] 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 5 mg/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, cholecystolithiasis, 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 35 g/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 20 mg daily, followed by oral prednisone 45 mg daily. Ciclosporin was administered at 100 mg twice daily. The patient responded to the treatment, with hemoglobin levels increasing steadily to 148 mg 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 1.92 g twice daily. However, the patient still had intermittent fever; thus, voriconazole (0.2 g

Editor: N/A.

The authors have no conflicts of interest to disclose.

[a] Department of Rheumatology and Immunology, Xiangya Hospital, [b] The Institution of Rheumatology and Immunology, Central South University, Changsha, Hunan, China.

[*] Correspondence: Sijia Liu, Department of Rheumatology and Immunology, Xiangya Hospital, Central South University, Changsha, Hunan, China, The Institution of Rheumatology and Immunology, Central South University, Changsha, Hunan, China (e-mail: 178844161@qq.com).

Medicine (2018) 97:40(e12716)

Received: 8 May 2018 / Accepted: 14 September 2018

http://dx.doi.org/10.1097/MD.0000000000012716

Table 1

Case description.

Refs.	Year	Nation	Type of HA	Sex	Age	Treatment
[7]	1980	United States	DIIHA	Female	53	Drug discontinuance
[8]	1990	Japan	DAT-negative AIHA	Male	64	Prednisolone
[9]	2008	India	Not mentioned	Female	42	Steroid

AIHA = autoimmune hemolytic anemia, DAT = direct antiglobulin test, DIIHA = drug-induced immune hemolytic anemia, HA = hemolytic anemia.

twice daily) was added and symptoms improved. The patient was maintained on SMZ and voriconazole for *Nocardia* infection, methylprednisolone 12 mg/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 (DIIHA) was excluded and mixed-type AIHA was diagnosed. The patient was treated with a 6-day course of intravenous immunoglobulin, 40 mg/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,[7] while mixed-typed 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.

Itabashi et al[3] reported a case that the patient developed AIHA the same time at RP onset. Both AIHA and RP improved rapidly after prednisolone administration. These facts indicated that AIHA may be hematological system involvement in the RP patient. However, the situation was different in our patient. She had developed hemolytic anemia twice, without any inducement. She was diagnosed with AIHA after autoantibodies were detected. Given the circumstance that her RP was stable and low-dose oral corticosteroids was enough to maintain remission, AIHA was considered irrelevant to RP and primary AIHA was diagnosed. The patient developed a third hemolytic anemia while she was under SMZ treatment for pulmonary nocardiosis. Although sulfonamides may induce hemolytic anemia,[10] this situation usually happens to patients with glucose-6-phosphate dehydrogenase deficiency, especially in newborns and children,[11] within 24 to 72 hours.[12] Our patient developed hemolytic anemia after 7 months of SMZ treatment. The dosage was reduced at that time. Furthermore, her anemia was improved after intravenous immunoglobulin and glucocorticoid treatment without withdrawing SMZ. Thus, DIIHA was excluded from the perspective of clinical manifestation and treatment effect and therefore a diagnosis of primary AIHA was made.

RP and AIHA have different pathogenesis. RP is a connective tissue disease primarily affecting proteoglycan-rich structures and cartilaginous tissues, especially the auricular pinna, cartilage of the nose, the tracheobronchial tree, the eyes, and the heart's connective components. The exact pathogenesis remains obscure. It seems to be a combination of genetic predisposition, a triggering factor, and presence of autoimmunity. In RP, HLA-DR4 acts as disease-susceptibility genes.[13] Resent research showed that HLA-DRB1*16:02, HLA-DQB1*05:02, and HLA-B*67:01 were associated with RP.[14] Triggering factors for RP include mechanical stimuli, such as local cartilage traumas[15] and ear piercing[16] that may expose cryptogenic antigens of the cartilaginous matrix. Glucosamine chondroitin supplement[17] and anti-TNF-α drugs[18,19] were considered to potentially initiate RP. Furthermore, infectious agents such as *Mycobacterium tuberculosis* and *Myxoma virus*, which share structural homology with cartilaginous autoantigens, may cross-react with autoantigens related to the disease.[20] Chronic hepatitis C virus infection may nonspecifically activate the immune system and thus trigger RP.[21,22] The autoimmune pathogenesis is hypothetically induced by the aforementioned precipitating factors, which expose connective tissue or cell membrane self-epitopes in genetically susceptible individuals. Several autoantibodies have been found in RP, including collagen type II,[23] matrilin 1,[24] cochlea, vestibule, and corneal epithelium. The subsequent inflammatory response would perpetuate enzymatic (especially MMP-3 and cathepsins L) and oxygen metabolite-mediated connective tissue degradation.[25] Cytokines released during this inflammatory process can both amplify the pathologic process, and induce constitutional symptoms.[26]

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 antibody-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

those with cold AIHA, the Ii blood group system is the most common target. The postulated mechanisms of the abnormal autoantibody producing including an immune response toward some cryptic antigens and/or a molecular mimicry with a cross-reactivity between external antigens and autoantigens, which is likely in RP. However, the mechanisms leading to the breakdown of self-tolerance, which may explain why our patient developed 2 autoimmune diseases, have not been fully elucidated. Notwithstanding, it has been hypothesized that alterations in the presentation of autoantigens on target cells could overcome self-tolerance. Several hypotheses attempt to explain the lack of effective presentation of autoantigens. One postulate is that the antigen presenting cells (APCs) remain relatively immature and therefore tolerate rather than activate self-reactive cells. The second is that many self-epitopes may be inefficiently processed and 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.[28] In addition, polyclonal activators such as superantigens or mitogens, which are associated with a failure to control lymphoproliferation may explain autoaggressive damaging tissue responses.[28]

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: Xiaoxia Zuo.
Writing – original draft: Qianyun Xu.
Writing – review & editing: Sijia Liu.

References

[1] Vitale A, Sota J, Rigante D, et al. Relapsing polychondritis: an update on pathogenesis, clinical features, diagnostic tools, and therapeutic perspectives. Curr Rheumatol Rep 2016;18:1–2.
[2] Waller E, Goehrs H. Dapsone-induced hemolytic anemia in a patient with relapsing polychondritis. Ann Pharmacother 1980;14:412–4.
[3] Itabashi H, Hishinuma A, Yoshida K, et al. A case of relapsing polychondritis associated with hemolytic anemia. Jpn J Med 1990;29:91–4.
[4] Ananthakrishna R, Goel R, Padhan P, et al. Relapsing polychondritis—case series from South India. Clin Rheumatol 2009;28:7–10.
[5] Hazra N, Dregan A, Charlton J, et al. Incidence and mortality of relapsing polychondritis in the UK: a population-based cohort study. Rheumatology 2015;54:2181.
[6] Ludvigsson JF, Ronald VV. Prevalence and comorbidity of relapsing polychondritis. Clin Epidemiol 2016;8:361–2.
[7] Eaton WW, Rose NR, Kalaydjian A, et al. Epidemiology of autoimmune diseases in Denmark. J Autoimmun 2007;29:1–9.
[8] Mayer B, Yürek S, Kiesewetter H, et al. Mixed-type autoimmune hemolytic anemia: differential diagnosis and a critical review of reported cases. Transfusion 2008;48:2229–34.
[9] Rattarittamrong E, Eiamprapai P, Tantiworawit A, et al. Clinical characteristics and long-term outcomes of warm-type autoimmune hemolytic anemia. Hematology 2016;21:368–74.
[10] Frieder J, Mouabbi JA, Zein R, et al. Autoimmune hemolytic anemia associated with trimethoprim-sulfamethoxazole use. Am J Health Syst Pharm 2017;74:894–7.
[11] Heeres PA, Zondag HA. [Hemolytic anemia caused by sulfanilamide as a result of glucose-6-phosphate-dehydrogenase deficiency: an x-chromosomal hereditary disease]. Folia Med Neerl 1961;4:121–31.
[12] Torres HA, Barnett BJ, Arduino RC. Use of fosamprenavir, a sulfa-containing protease inhibitor, in HIV-infected patients with glucose-6-phosphate dehydrogenase deficiency. Clin Infect Dis 2007;44:887–8.
[13] Lang B, Rothenfusser A, Lanchbury JS, et al. Susceptibility to relapsing polychondritis is associated with HLA-DR4. Arthritis Rheum 1993;36:660–4.
[14] Terao C, Yoshifuji H, Yamano Y, et al. Genotyping of relapsing polychondritis identified novel susceptibility HLA alleles and distinct genetic characteristics from other rheumatic diseases. Rheumatology (Oxford) 2016;55:1686–92.
[15] Cañas CA, Fabio BA. Local cartilage trauma as a pathogenic factor in autoimmunity (one hypothesis based on patients with relapsing polychondritis triggered by cartilage trauma). Autoimmune Dis 2012;2012:453698.
[16] Alissa H, Kadanoff R, Adams E. Does mechanical insult to cartilage trigger relapsing polychondritis? Acta Rheumatol Scand 2001;30:311.
[17] Furer V, Wieczorek RL, Pillinger MH. Bilateral pinna chondritis preceded by glucosamine chondroitin supplement initiation. Scand J Rheumatol 2011;40:241–3.
[18] Azevedo VF, Galli NB, Kleinfelder ADF, et al. Relapsing polychondritis in a patient with ankylosing spondylitis using etanercept. Case Rep Rheumatol 2014;2014:353782.
[19] Hernández MV, Ruizesquide V, Gómezcaballero ME, et al. Relapsing polychondritis: a new adverse event secondary to the use of tumour necrosis factor antagonists? Rheumatology 2011;50:1523–5.
[20] Menge T, Rzepka R, Melchers I. Monoclonal autoantibodies from patients with autoimmune diseases: specificity, affinity and crossreactivity of MAbs binding to cytoskeletal and nucleolar epitopes, cartilage antigens and mycobacterial heat-shock protein 60. Immunobiology 2002;205:1–6.
[21] Alvi S, Magrey MN. Polychondritis associated with chronic hepatitis C virus infection. J Rheumatol 2011;38:2281–2.
[22] Hemmati I, Yoshida E, Shojania K. Relapsing polychondritis associated with hepatitis C virus infection. Clin Rheumatol 2012;31:391–4.
[23] Ebringer R, Rook G, Swana GT, et al. Autoantibodies to cartilage and type II collagen in relapsing polychondritis and other rheumatic diseases. Ann Rheum Dis 1981;40:473–9.
[24] Hansson AS, Heinegård D, Piette JC, et al. The occurrence of autoantibodies to matrilin 1 reflects a tissue-specific response to cartilage of the respiratory tract in patients with relapsing polychondritis. Arthritis Rheum 2001;44:2402–12.
[25] Ouchi N, Uzuki M, Kamataki A, et al. Cartilage destruction is partly induced by the internal proteolytic enzymes and apoptotic phenomenon of chondrocytes in relapsing polychondritis. J Rheumatol 2011;38:730.
[26] Stabler T, Piette JC, Chevalier X, et al. Serum cytokine profiles in relapsing polychondritis suggest monocyte/macrophage activation. Arthritis Rheum 2004;50:3663–7.
[27] Nomura S, Okamae F, Matsuzaki T, et al. Autoimmune hemolytic anemia and HLA-DQ6. Autoimmunity 1998;28:57–8.
[28] Barros MM, Blajchman MA, Bordin JO. Warm autoimmune hemolytic anemia: recent progress in understanding the immunobiology and the treatment. Transfus Med Rev 2010;24:195–210.