Coombs-negative Autoimmune Hemolytic Anemia Followed by Anti-erythropoietin Receptor Antibody-associated Pure Red Cell Aplasia: A Case Report and Review of Literature

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Abstract

A 76-year-old woman was referred to our hospital because of anemia. The laboratory findings revealed hemolysis. Although a direct Coombs test was negative, a high titer of RBC-bound IgG was detected, and a diagnosis of Coombs-negative autoimmune hemolytic anemia was made. She was successfully treated with prednisolone. One year and five months later, she again presented anemia and was diagnosed with pure red cell aplasia. Anti-erythropoietin receptor antibody was detected in the serum. She was treated with cyclosporine and obtained prompt recovery. We herein report this rare case and review the pertinent literature.

Key words: autoimmune hemolytic anemia, pure red cell aplasia, anti-erythropoietin receptor antibody, cyclosporine


Introduction

Both autoimmune hemolytic anemia (AIHA) and pure red cell aplasia (PRCA) are rare hematological disorders. The etiology of these diseases is not yet well understood; however, abnormal immune reactions might be responsible for their development. AIHA is a disease in which autoantibodies against autologous red blood cell (RBC) membrane proteins are produced, which shortens the survival of RBCs. The cause of AIHA is idiopathic or secondary. Secondary AIHA is associated with malignancies, such as lymphoma, leukemia or ovarian tumors; with autoimmune disorders, such as systemic lupus erythematosus (SLE) or ulcerative colitis; and with drugs, such as α-methyldopa (1). PRCA is a disease in which the numbers of erythroid progenitors in the bone marrow are reduced but granulopoiesis and megakaryopoiesis are normal. There are two main types of PRCA: a congenital type (Diamond-Blackfan anemia) and an acquired type. The acquired type of PRCA, can be associated with infections such as parvovirus B19, autoimmune diseases and neoplasms such as thymoma, lymphoma or carcinoma; it can also be idiopathic (2). Although the pathogenesis of PRCA is not yet well known, various autoimmune mechanisms have been described, such as the production of antibodies against erythroid progenitors or erythropoietin (EPO). Cellular immunity is also proposed to be involved in the pathogenesis, through the direct or indirect injury of erythroblasts, by T cells or natural killer cells.

Although rare, the simultaneous or sequential occurrence of PRCA and AIHA has been the subject of several reports (3-19). This indicates that there are some mechanisms that occur in the pathogenesis of these diseases. Recently, a case of a malignant lymphoma patient in whom PRCA was accompanied by Coombs-negative AIHA was reported in which the PRCA was found to be anti-EPO receptor antibody-associated (20). We herein report a case of primary Coombs-negative AIHA followed by anti-EPO receptor antibody-associated PRCA and discuss the basis of the patient’s pathological status.

Case Report

A 76-year-old woman was referred to our hospital because of anemia. She had a medical history of diabetes mellitus with under good control and was not be treated with
any medications. The peripheral blood laboratory data were as follows: WBC 2,700/μL, Hb 6.1 g/dL, reticulocyte 7.1 %, platelets 16.9×10⁴/μL, lactate dehydrogenase (LDH) 236 U/L, T.Bil 1.8 mg/dL. The patient’s haptoglobin of <10 mg/dL was under the detection level. Bone marrow aspiration revealed erythroid hyperplasia and abdominal ultrasonography indicated splenomegaly. There was no lymph node swelling. Although a direct Coombs test was negative, 76 RBC-bound IgG on 1 RBC (normal range, 33±13) indicated that the patient had Coombs-negative AIHA (21). She was treated with prednisolone (50 mg/day) and promptly recovered (Figure). However, after one year and 5 months, severe anemia (Hb 4.7 g/dL) appeared while she was still taking a reduced dose of prednisolone (5 mg/day). Reticulocytopenia (0.3%, 7,140/μL) was observed in the peripheral blood and marked erythroid hypoplasia was observed in the bone marrow. A cytogenetic analysis of the bone marrow was normal. Based on the findings, the patient was diagnosed with PRCA. At this time, the patient’s laboratory data were as follows: LDH 150 U/L, T.Bil 0.7 mg/dL and haptoglobin 21 mg/dL. Parvovirus B19 infection was not detected by a serological test for anti-parvovirus B19 IgM antibody. No abnormalities (including thymoma and other abnormalities) were detected by systemic contrast-enhanced computer tomography and no monoclonal lymphocytes were detected by a polymerase chain reaction (PCR) to investigate the immunoglobulin heavy chain and T cell receptor β chain rearrangement in the peripheral blood. The drugs that the patient took when the PRCA occurred included esomeprazole, prednisolone, voriconazole, linagliptin (after starting prednisolone treatment), and risedronate. All of the drugs, with the exception of voriconazole had been administered for more than one year. Voriconazole was administered for three months before the onset of PRCA because of a slight increase in the serum level of aspergillus antigen. To examine the cause of PRCA, the serum level of anti-erythropoietin receptor antibody was measured by an enzyme-linked immunosorbent assay which indicated a positive result with an optical density (OD₄₅₀) of 1.647 (normal range, <1.5) (22). Cyclosporine therapy was started at a dose of 150 mg/day 6 weeks after the diagnosis of PRCA. Reticulocytosis appeared 10 days after the start of treatment and the patient’s anemia promptly recovered (Figure).

Discussion

There are several reports of cases in which both AIHA and PRCA occurred simultaneously or sequentially (3-19). Table is a list of the published reports. Usually, this occurs in association with other diseases, including: hematological malignancies such as lymphoma (6, 8, 20) and chronic lymphocytic leukemia (15); autoimmune diseases such as Sjögren syndrome (9, 11, 17) and SLE (13); infections such as hepatitis (19); or due to the use of immunosuppressive drugs after transplantation, such as alemtuzumab (10, 14). Although rare, cases of primary AIHA followed by PRCA that are not associated with other have been reported (3, 7, 12, 16). The diagnosis of the patient of our present case is also considered to be primary AIHA followed by PRCA. Although the precise mechanism by which these rare diseases occur together or sequentially remains to be elucidated, several studies have explored the pathogenesis. In a case of chronic lymphocytic leukemia (CLL), a parvovirus B19 infection was considered to have caused PRCA (15), while anti-EPO antibody caused the PRCA in a patient with SLE (13). In a case of primary AIHA followed by PRCA, the cytotoxic mononuclear cells directly affected the erythroid precursors and caused PRCA (3). Recently, Fujimi et al. reported a case of anti-EPO receptor antibody-associated PRCA that was accompanied by Coombs-negative AIHA in a lymphoma patient (20). The anti-EPO receptor antibodies are newly identified autoantibodies that are associated with the pathogenesis of anemia (22). In our case, the patient’s serum was positive for anti-EPO receptor antibody when the PRCA occurred; thus this was a potential cause of the PRCA. Drug use sometimes causes PRCA. In our case, with the exception of voriconazole, the drugs that the patient was taking when PRCA occurred had been ad-
ministered for more than one year, thus it seems unlikely that the patient’s condition was related to the administration of these drugs. The administration of voriconazole was started three months before the onset of PRCA. Although the myelosuppression and aplastic anemia are rare side effects of voriconazole administration, the possibility that voriconazole was the cause of the patient’s PRCA cannot totally be denied. To the best of the authors’ knowledge, this is the second report to describe the association between PRCA following AIHA and anti-EPO receptor antibody positivity (20). Furthermore, this is the first report in relation to PRCA with primary AIHA. Because the method for detecting anti-EPO receptor antibody was recently developed, it is possible that anti-EPO receptor antibody might have been the cause of PRCA in some of the cases in which both AIHA and PRCA occurred. Why both AIHA and PRCA occur at the same time or sequentially is a puzzle. The target antigens in AIHA are the membrane proteins of mature RBCs. On the other hand, the target antigens in PRCA are the molecules that are expressed in precursor erythroblasts. In some cases there might be the mechanisms that bridge these erythroid cells, such as antigen drift from mature RBCs to precursor erythroid cells during dysregulated autoimmune responses. The further accumulation of such cases and analyses to investigate the associated immune dysregulation are needed.

The Coombs test of the patient of our present case was negative (23). In the reported cases in which both AIHA and PRCA occurred, the ratio of Coombs-negative AIHA was approximately 30%; thus, in this pathological status, the negative rate of the Coombs test might be high. However, the number of reported cases is very small. As a result, this might be an issue in the future.

In conclusion, we herein reported a rare case of primary AIHA followed by anti-EPO receptor antibody-associated PRCA. We hope that the pathological mechanisms of such patients will be elucidated in the near future.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

The authors would like to thank Dr. Akinori Hara and Takashi Wada at the Department of Nephrology, Kanazawa University Hospital, Kanazawa, Japan, for measuring of the anti-EPO receptor antibody levels, and Dr. Toyomi Kameishi at the Center for Community Medicine, Jichi Medical University, Tochigi, Japan, for measuring the RBC-bound IgG levels.

References


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**Table. Published References of AIHA and PRCA.**

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