Burkitt Lymphoma Preceded by Autoimmune Hemolytic Anemia due to Anti-D Antibody

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Abstract

We herein report a rare case of Burkitt lymphoma (BL) preceded by autoimmune hemolytic anemia (AIHA) caused by autoantibodies against D antigen. After a partial response to AIHA with prednisolone (PSL) treatment for 7 months, the patient developed BL with a t(8;22)(q24;q11.2) chromosomal translocation. Intensive immunochemotherapy, including rituximab, led to a complete response (CR) of BL; however, anti-D antibody remained detectable in the plasma and antibody-dissociated solution from erythrocytes, thus continuous therapy with PSL was necessary even after achievement of the CR. BL with AIHA is extremely rare, with only one previously reported case in the literature.

Key words: Burkitt lymphoma, autoimmune hemolytic anemia, anti-D antibody

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Introduction

Autoimmune hemolytic anemia (AIHA) is caused by the development of autoantibodies against various types of surface antigens on red blood cells. AIHA generally emerges as a sporadic and idiopathic benign hematologic disease and occasionally as a paraneoplastic symptom (1). In particular, lymphoid malignancies [i.e., certain disease subtypes of non-Hodgkin’s lymphomas (NHLs) or chronic lymphocytic leukemia] often underlie the development of AIHA (2). Therefore, a careful systemic search for the co-existence of subclinical lymphoid malignancies is essential in the diagnosis of AIHA, especially in steroid-resistant cases. Burkitt lymphoma (BL), which accounts for less than 1.0% of all NHLs, is characterized by disease-specific chromosomal translocation involving c-Myc gene rearrangement (3, 4). The clinical behavior of BL is generally aggressive, presenting with a bulky mass, B symptoms, or invasion as an extra-nodular lesion in the bone marrow or the central nervous system, however, BL has rarely been associated with autoimmune symptoms. Indeed, there is only one case of cold agglutinin disease associated with BL in the English literature (5). We herein report a rare case of BL that developed during corticosteroid treatment for AIHA caused by anti-D antibody.

Case Report

A 67-year-old woman first consulted a local hospital complaining of general fatigue. At her first visit, blood tests revealed severe anemia according to a hemoglobin (Hb) level of 5.5 g/dL (normal range: 11.7-15.1 g/dL); an increased mean cell volume (MCV) of 119.7 fL (normal range: 85.9-97.4 fL); increased peripheral reticulocytes (194.3×10⁹/L) with a normal leukocyte count [5.6×10⁶/L; normal range: 3.4-7.3 (×10⁶/L)] (neutrophils 84%, lymphocytes 5%, monocytes 4%) and a normal platelet count [225.0×10⁹/L; normal

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range 150.0-350.0×10^9/L); elevated serum lactate dehydrogenase (LDH) (407 U/L; normal range: 114-243 U/L), decreased serum haptoglobin below the level of detection (normal range: 19-200 mg/dL); and elevated serum indirect bilirubin (2.3 mg/dL; normal range 0.2-1.2 mg/dL). Her blood type was AB and RhD-positive. Direct and indirect Coombs tests were positive, a cold hemagglutination test was negative, and serum monoclonal immunoglobulin was absent. A direct antiglobulin test revealed only IgG detectable on red blood cells (RBCs) without reaction to complement 3 (C3). Neither malignant disease nor splenomegaly was evident in routine systemic work-up assessments, including gastrointestinal endoscopy and systemic computed tomography (CT).

The patient had been treated for paroxysmal atrial fibrillation with warfarin and pilsicainide for 17 years. She had given birth to two children in her twenties and had never received a RBC transfusion. A bone marrow analysis showed relative erythroblast hyperplasia without the presence of abnormal or dysplastic cells. According to these findings, the patient was initially diagnosed with idiopathic AIHA. Treatment with 50 mg/day of prednisolone (PSL) initially induced partial remission of AIHA and was gradually reduced to 4 mg/day within four months. However, the disease then worsened and PSL was increased to 25 mg/day to avoid worsening of anemia.

After a 7-month course of AIHA treatment with PSL, the patient simultaneously developed a walnut-sized thyroid mass with left cervical lymphadenopathy and abdominal distention with epigastric pain and was referred to our hospital for further examination and treatment. At this admission, the Eastern Cooperative Oncology Group performance status was grade 2. A systemic CT scan detected lymphadenopathy in the cervical, mediastinal and perigastric lymph nodes, a thyroid mass, gastric wall thickening, pleural effusion, and massive ascites (Fig. 1). Endoscopy also revealed the presence of gastric lymphoma (Fig. 2A).

Laboratory tests at this time again revealed several abnormal findings, including macrocytic anemia (Hb 7.5 g/dL) with a MCV of 109.9 fl, increased peripheral reticulocytes, an increased leukocyte count (14.1×10^6/L) (neutrophils 97%, lymphocytes 1%, monocytes 2%), elevated serum LDH (742 U/L), decreased serum haptoglobin below the level of detection, and elevated serum soluble interleukin-2 receptor (2,820 U/mL; normal range: 145-519 U/mL). The patient was negative for human immunodeficiency virus infection. A bone marrow (BM) analysis showed normoplastic hematopoiesis without invasion of abnormal cells, while a chromosomal analysis of BM metaphase cells by Giemsa banding identified a constitutional abnormality of 46,XX,inv(8)(p21q11.2)c [20/20].

A histologic examination of samples from a cervical lymph node biopsy revealed diffuse proliferation of abnormal lymphoid cells that were positive for CD10, CD20 and BCL6, but negative for BCL2, CD3, CD5 and CD21. Tingley body macrophages were scattered, showing a “starry sky” appearance (Fig. 3). An immunophenotypic analysis of the biopsied specimen by flow cytometry also showed that the malignant cells were positive for CD10, CD19, CD20, CD45, surface immunoglobulin G (sIgG) and lambda light
chain, but negative for CD3, CD5 and CD23. Nearly all tumor cells were positive for MIB1, indicating a high proliferative potency, but negative in EBER-ISH [Epstein-Barr virus (EBV) encoded small RNA in situ hybridization], excluding latent EBV infection in tumor cells. A cytogenetic analysis revealed an abnormal karyotype: 45,X,-X,add(1) (q24),inv(8)(p21q11.2),t(8;22)(q24;p11.2) [20/20] (Fig. 4).

At this time, we also re-evaluated the immunologic fea-
Figure 4. A G-banding analysis of the lymph node biopsy samples showed an abnormal karyotype: 45,X,-X,add (1) (q24), inv (8) (p21q11.2) c,t (8;22) (q24;p11.2) [20/20].

...tures of AIHA in this case. Direct and indirect Coombs tests remained positive, and the Rh blood group was confirmed to be CcDEe. In the presence of polyethylene glycol (PEG) enhancement, anti-D antibodies were 512- and 256-fold positive in the plasma and antibody-dissociated solution from erythrocytes, respectively, suggesting a large amount of anti-D in the plasma after reaction to RBCs. Additional screening tests detected no other antibodies in the plasma, while broad and non-specific autoantibodies were detectable at lower titers in dissociated solution from erythrocytes. Typing of RhD antigen using the Advanced Partial RhD Typing Kit (Alba Bioscience, Edinburgh, UK) indicated that the patient did not harbor a partial D or weak D phenotype, which may cause alloimmunity for RhD antigen. Furthermore, the activities of her plasma against RhD-negative panel RBCs were all negative, suggesting the absence of an antibody against RhD-mimicking antigen, including the Landsteiner-Wiener (LW) antibody. These results indicated that acquired autoimmunity against RhD antigen was the most likely cause of hemolytic anemia. According to these findings, the patient was diagnosed with BL, stage IV (P) according to the Ann Arbor staging system, preceded by AIHA.

To reverse the rapid deterioration of her physical condition due to progressive disease, R-CHOP [rituximab (RIT), cyclophosphamide (CPA), doxorubicin (DOX), vincristine (VCR), PSL] therapy was initiated as soon as the tentative diagnosis of B-cell lymphoma was made according to the results of the immunophenotypic analysis of tumor cells by a flow cytometric analysis on the day of biopsy. The first course of R-CHOP induced a partial response. The final diagnosis of BL was confirmed after the single course of R-CHOP, and the patient was subsequently treated with six courses of dose-adjusted EPOCH-R (RIT, DOX, etoposide, VCR, CPA, PSL), which induced a complete response (CR) (Fig. 2B, 5). During the treatment of BL, we continued immunosuppressive therapy with PSL and RhD-negative red cell transfusion as needed. The dose of PSL of 20 mg/day at admission was tapered to 10 mg/day before discharge. Despite the achievement of a CR of BL, anti-D antibody remained detectable in the plasma and antibody-dissociated solution from erythrocytes (Fig. 6).

The prevalence of AIHA has been reported to range from 0.23% to 6.2% in patients with NHL. A literature search for NHL associated with AIHA identified 91 cases reported between 1968 and 2007, of which 10 involved associations of warm antibody AIHA with high grade B-cell lymphoma (2). Among lymphoproliferative diseases, AIHA occurs most frequently in chronic lymphocytic leukemia (6). Very little is known about the clinical features of AIHA in patients with
Figure 5. CT images showed the disappearance of the cervical (A), mediastinal (B), and perigastric (C) lymph nodes, gastric wall thickening (C), and ascites (C, D) after chemotherapy.

Figure 6. The treatment course showing the transition of hemolytic anemia and the anti-D antibody level, along with chemotherapy. Anti-D Ab: anti-D antibody, Hb: hemoglobin, Rh (D): RBC BT: Rh (D) negative red blood cell transfusion, wk: week

BL, with only one previous case report available.

In our patient, AIHA symptoms were apparent for 7 months before the diagnosis of BL. However, a routine work-up at the time of the initial AIHA diagnosis overlooked the presence of an initial minimal lesion of BL, and therefore it is unclear if BL or AIHA developed first. The
diagnosis of AIHA often precedes the diagnosis of NHL, even when AIHA develops as a complication of primary NHL and particularly in cases of indolent lymphomas (7). However, it appears less likely that BL, which is a highly aggressive lymphoma, remained asymptomatic in our patient for 7 months. Another possibility is that BL developed due to immune dysregulation and immunosuppressive therapy, however, there has been no previous report of BL associated with an autoimmune condition. The major types of NHL associated with autoimmune conditions include diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia, small lymphocytic leukemia, marginal zone lymphoma and peripheral T cell lymphoma (8, 9). It is therefore difficult to draw the conclusion that immune dysregulation in association with AIHA and immunosuppressive therapy led to BL in our patient.

We initiated chemotherapy with R-CHOP according to the tentative diagnosis of B-cell lymphoma immediately after the biopsy due to a rapid progression of the disease. The patient was subsequently treated with dose-adjusted EPOCH-R because histological and immunophenotypical assessments and the presence of a t(8;22)(q24;q11.2) chromosomal translocation led to a final diagnosis of BL. Although the expression of sIgM or IgD on tumor cells is more common in BL, the expression of sIgG (or sIgA), as in our case, has also been observed with BL (10). In AIHA associated with high-grade B-cell lymphoma, chemotherapy against lymphoma may have better efficacy for typical primary AIHA compared to established treatments, including PSL, immunoglobulin and splenectomy (2). However, the treatment of BL did not cure AIHA in our patient, which suggests that BL was not directly causative in the development of AIHA. Hence, the possibility that AIHA and BL occurred independently of each other could not be excluded in our patient.

A transient and marked reduction of anti-D antibody in the plasma occurred in the initial four weeks of immunochemothrapy. The level of plasma anti-D antibody is determined by the balance between its production and consumption. At least two factors might be associated with the reduction in the anti-D antibody level: rapid consumption of the antibody by patient-derived RhD-positive erythrocytes, concomitant with reduced antibody production due to intensive immunochemothrapy containing RIT. The subsequent re-elevation of anti-D antibody in the plasma presumably occurred because production of the antibody overwhelmed consumption by residual RhD-positive erythrocytes following repeated RhD-negative RBC transfusion during the initial phase of treatment, despite the decrease in antibody production.

In conclusion, the molecular mechanism of the association between AIHA and lymphoma remains to be fully determined, particularly with respect to AIHA with BL, and a greater accumulation of studies on the management of AIHA associated with BL is required.

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

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