Case Reports

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Other iatrogenic immunodeficiency lymphoproliferative disorder induced by corticosteroid used for an autoimmune disorder

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Abstract

Other iatrogenic immunodeficiency lymphoproliferative disorders (oii-LPD) are defined as lymphoid proliferations or lymphomas that occur in patients taking immunosuppressive agents (ISA) for autoimmune disorders (AID). Although methotrexate and tumor necrosis factor-alpha inhibitors cause oii-LPD, the association between corticosteroids and lymphomagenesis remains unknown. Herein, we present the case of a 51-year-old woman with oii-LPD caused by corticosteroid use for autoimmune hemolytic anemia (AIHA). The diagnosis of AIHA was made in May 2016, and AIHA had been well-controlled for 5 years with oral prednisolone (PSL). During a regular follow-up visit in March 2022, an abnormal increase in atypical lymphoid cells in the peripheral blood was found. The bone marrow biopsy specimens showed local aggregations of large cells that were identified as lymphoplasmacytic cells and plasma cells, and that were positive for cluster of differentiation (CD)19 and CD20, with apparent nucleoli among the diffuse infiltration of atypical small lymphocytes. The large cells were partially positive for the Epstein–Barr encoding region *in situ* hybridization and latent membrane protein 1, which confirmed Epstein–Barr virus (EBV)-affected lymphomagenesis. To our knowledge, this is the first report of an oii-LPD case shown to be induced by corticosteroid use for AID.

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Introduction

The occurrence of lymphoproliferative disorders (LPD) is associated with an immunodeficient status, such as primary immune disorder, human immunodeficiency virus (HIV) infection, post-transplant recipient, and the use of immunosuppressive agents (ISA).[1–6] LPD associated with ISAs was defined as other iatrogenic immunodeficiency LPD (oii-LPD).[1] Methotrexate, tumor necrosis factor-alpha inhibitors (TNFi), and other ISAs cause LPD involved with the Epstein–Barr virus (EBV).[2,3] However, the association between corticosteroid use and lymphomagenesis remains unknown, although several studies have suspected that using corticosteroids for autoimmune disorders (AID) and allergic diseases can increase the risk of lymphoma.[4–6] Herein, we present the case of a woman with oii-LPD caused by corticosteroid use for autoimmune hemolytic anemia (AIHA). To our knowledge, this is the first report of oii-LPD caused by corticosteroid use for an AID.

Case report

The reporting of this study conforms to the CARE guidelines.[7]

A 51-year-old woman who used oral prednisolone (PSL) for AIHA for 5 years had an elevated white blood cell count with leukemic atypical lymphocytes and a monoclonal paraprotein during a regular follow-up visit in March 2022. The diagnosis of AIHA was made in May 2016, with no evidence of lymphoma. She had a normal serum immunoglobulin level, physical and radiological findings revealed no lymphadenopathy and splenomegaly, and conventional cytogenetic analysis of the bone marrow (BM) showed the normal karyotype. The initial dose of oral PSL was 1 mg/kg daily, and the dosage was tapered gradually and finally maintained at 10 mg daily. During the visit in March 2022, no physical complaints were recognized; however, the laboratory findings were as follows: white blood cell count: 24×10^9/L (atypical lymphocytes: 76%), hemoglobin: 132 g/L, platelet count: 78×10^9/L, lactate dehydrogenase: 391 IU/L (normal range: 124–222 U/L), C-reactive protein: 0.0027 g/L, immunoglobulin (Ig)G: 6.14 g/L, IgA: 5.03 g/L (normal range: 0.93–3.93 g/L), and IgM: 0.58 g/L. Computed tomography demonstrated moderate splenomegaly (Figure 1a) and no lymph node enlargement. The serum immunofixation electrophoresis test revealed monoclonal bands of IgA and lambda light chain (Figure 1b). The G-banding and spectral karyotyping analysis of the BM aspirates demonstrated 46,X, del(X)(q?), der(13)t(12;13)(q13:p11.2) [11/20 cells], and 46,XY [9/20 cells] (Figure 1c). May–Giemsa staining of the BM aspirates revealed the infiltration of various forms of small to large atypical lymphocytes, plasmacytoid lymphocytes, and plasma cells (Figure 2a and b). The BM biopsy specimens exhibited local aggregations of large cells with apparent nucleoli among the diffuse infiltration of atypical small lymphocytes, lymphoplasmacytic cells, and plasma cells (Figure 2c). Immunohistochemical staining showed that the atypical small to large

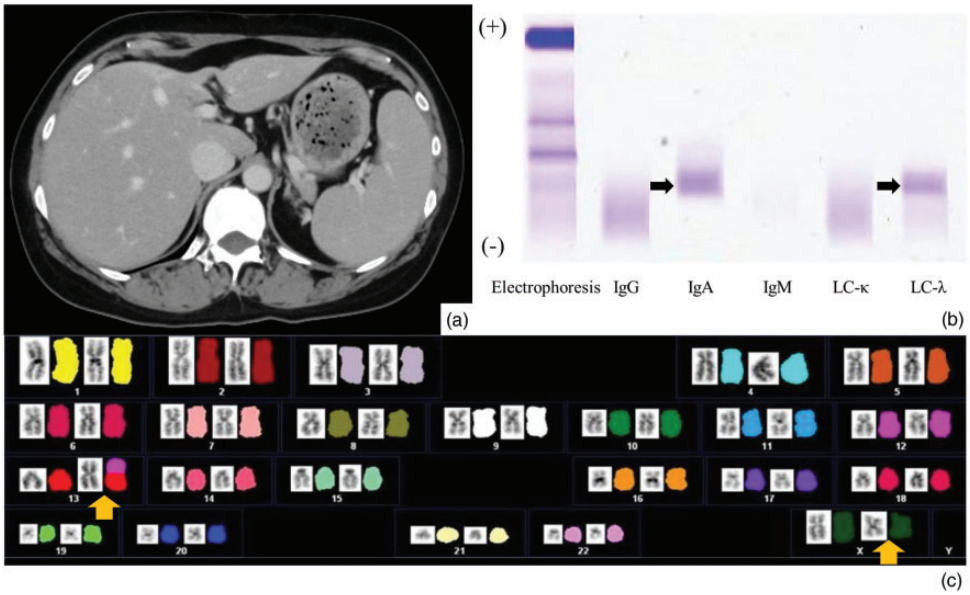

Figure 1. Imaging, serum immunofixation testing, and karyotypic analysis of the bone marrow. (a) Computed tomography image obtained at diagnosis showing splenomegaly. (b) Serum immunofixation electrophoresis test results. The arrows indicate monoclonal bands of IgA and lambda light chains and (c) Karyotyping test results for the BM aspiration specimens. The left side represents reverse DAPI staining, and the right side represents spectral karyotyping. The arrows indicate the abnormal chromosomes: del(X)(q?), der(13)t(12;13)(q13:p11.2). IgA, immunoglobulin A; BM, bone marrow; DAPI, 4′, 6-diamidino-2-phenylindole.

lymphocytes and lymphoplasmacytic cells were positive for cluster of differentiation (CD)19, CD20 (Figure 2d), and CD5, whereas the lymphoplasmacytic cells and plasma cells were positive for CD138 (Figure 2e). Large cells with nucleoli were partially positive with Epstein–Barr encoding region *in situ* hybridization (EBER-ISH) (Figure 2f) and for latent membrane protein 1 (LMP-1) (Figure 2g). The Ki-67 positivity rate was 60% in the large cell areas (Figure 2h). Considering these findings, the main involved lesions of the neoplastic cells were the BM and spleen. The neoplastic cells comprised large B-cells and small to medium-sized B-cells with plasma cell differentiation and IgA-monoclonal paraprotein. Therefore, transformation to aggressive B-cell lymphoma from indolent B-cell lymphoma with monoclonal IgA protein, such as in lymphoplasmacytic cell lymphoma (LPL) (non-Waldenström macroglobulinemia type LPL) or splenic marginal zone lymphoma, was considered an appropriate histopathological diagnosis. Furthermore, considering the history of long-term corticosteroid use in addition to the EBER positivity in the large neoplastic cells, the patient was diagnosed as having oii-LPD.

Severe BM damage was recognized; thus, immediate chemoimmunotherapy was required.[8] The patient achieved remission after six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) therapy.

Discussion

Immunodeficiency-associated LPDs include LPD associated with primary immune

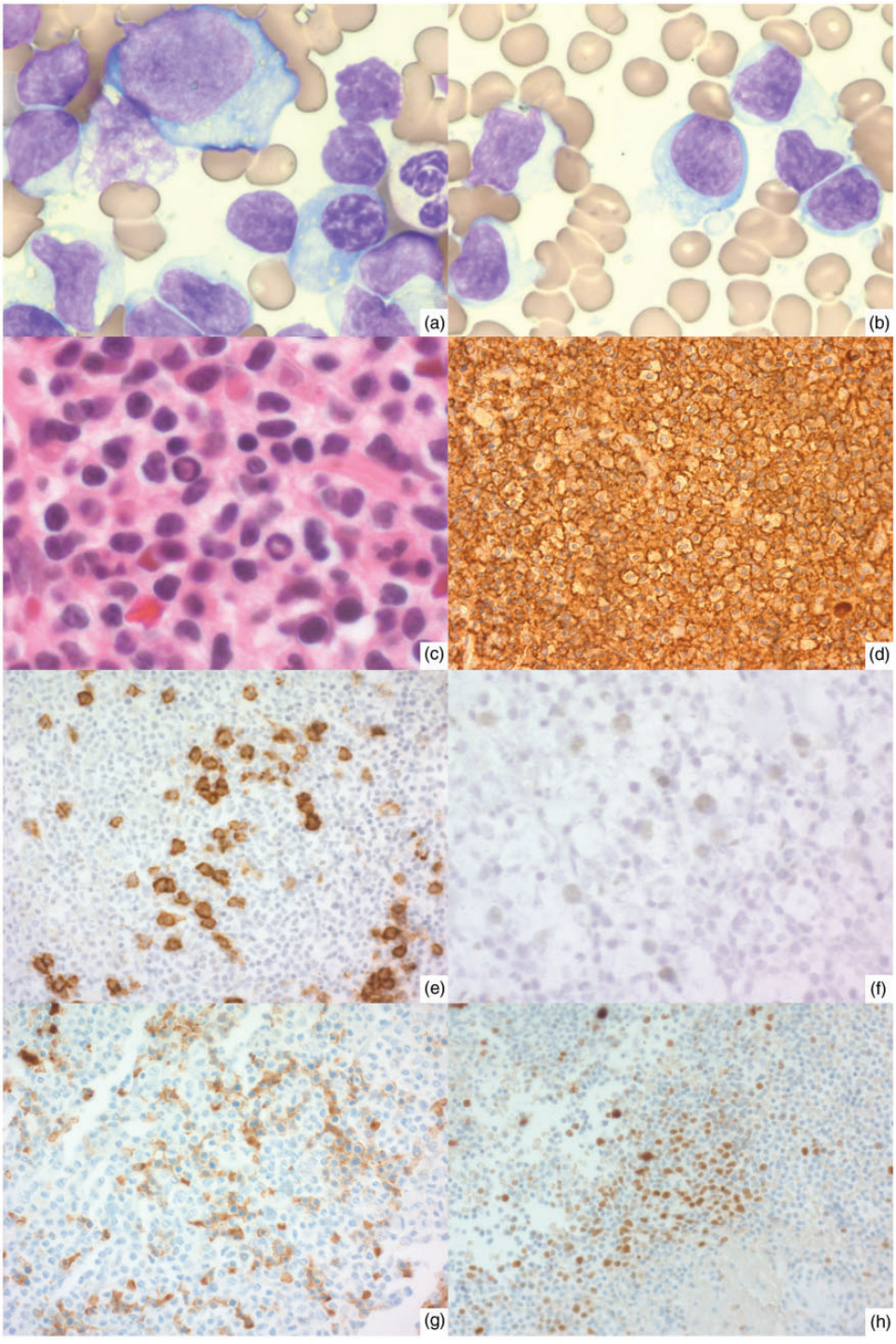

Figure 2. Results of bone marrow aspirates and biopsied specimens. (a) and (b) May–Giemsa staining of the BM aspiration specimens. (a) Large atypical lymphocytes, small atypical lymphocytes, and plasma cells

Continued.

disorders, lymphoma associated with HIV infection, post-transplant LPD, and oii-LPD.[9] oii-LPD is defined as lymphoid proliferation or lymphoma that occurs in patients taking ISAs for AIDs, according to the 4th edition of the World Health Organization (WHO) classification.[1] Methotrexate was one of the first ISAs reported to be associated with LPD,[10] and other ISAs, such as TNFi, calcineurin inhibitors, and azathioprine for AIDs, were also reported to cause LPD.[3,11–14] Reports that demonstrate an increased risk of LPD with corticosteroids for AIDs are rare, even though corticosteroids are widely used as ISAs.

Nationwide cohort studies using the data from the UK Biobank cohort and the Swedish Cancer Registry demonstrated that AIDs can increase the risk of cancer, especially lymphoma.[5,6] Notably, the increased risk of lymphoma was the highest with AIHA (the standardized incidence ratio was 27.2 (95% confidence interval (CI): 21.5–34.0)) among AIDs.[5] Regarding treatment for AIHA, corticosteroids are used as the first-line therapy,[15] and most patients with AIHA receive this therapy for a prolonged period. Recently, corticosteroid use was demonstrated to increase the risk of lymphoma in a case–control study using the United Kingdom Clinical Practice Research Datalink database.[4] Thus, higher exposure to corticosteroids in patients with AIHA, more so than with other AIDs, could increase the incidence of LPD. In the present case, no evidence of lymphoma was recognized at the time of AIHA diagnosis. Furthermore, long-term oral PSL was the only medication administered after the diagnosis of AIHA, and EBER positivity in the large neoplastic cells supported the diagnosis of oii-LPD. Additionally, the histopathological features indicated transformation to aggressive B-cell lymphoma from indolent B-cell lymphoma, with monoclonal IgA protein, although the possibility of the co-existence of LPD at the time of the diagnosis of AIHA could not be completely ruled out.

The following underlying mechanisms for lymphomagenesis in AID or allergy patients have been proposed:[5] 1) AIDs and lymphoma may share dysregulated B-cells, and disturbance of the signals that regulate B-cell activities and proliferation can cause pathogenic autoimmunity and lymphomagenesis; 2) secondary inflammation that is caused by repeated stimulation of autoimmunity, cytokines, or infections such as EBV, HIV, and hepatitis C virus; and 3) genetic factors (germline and somatic mutations) and epigenetic mechanisms can influence allergic diseases and lymphomas. In the present case, EBV may have been involved in lymphomagenesis with long-term PSL therapy for AIHA.

In summary, in addition to AIDs, ISAs, including corticosteroids, can increase the

Figure 2. Continued.
(original magnification ×640). (b) Lymphoplasmacytic cells and small atypical lymphocytes (×640). (c)–(h) Neoplastic cells in the BM biopsy specimens. (c) Hematoxylin and eosin staining. Diffuse infiltration of atypical lymphocytes, lymphoplasmacytic cells, and plasma cells. Dutcher bodies are visible among the neoplastic cells (×400). (d) Staining for CD20. The neoplastic lymphocytes stained positive for CD20 (×400). (e) Staining for CD138. The lymphoplasmacytic cells and plasma cells stained positive for CD138 (×640). (f) Staining for EBER-ISH. The nuclei of the large atypical lymphocytes stained positive for EBER-ISH (×400). (g) Staining for LMP-1. The cell membranes of the neoplastic lymphocytes stained positive for LMP-1 (×400) and (h) Staining for Ki-67. The Ki-67 positivity rate was 60% to 70% in the large-cell aggregations (×200).
BM, bone marrow; CD20, cluster of differentiation 20; CD138, cluster of differentiation 138; EBER-ISH, Epstein–Barr encoding region in situ hybridization; LMP-1, latent membrane protein-1.

risk of lymphoma. The present case indicated that lymphoma should be considered carefully during the course of treatment for AIDs, and using only corticosteroids may increase the risk of oii-LPD.

Declaration of conflicting interests

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Ethics and patient consent statement

Written informed consent for treatment and for publication of this report were obtained from the patient. Ethics committee approval was not required because this is a case report.

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