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Case Report

Autoimmune lymphoproliferative syndrome: the intermediate state between autoimmune diseases of blood system and diffuse large B-cell lymphoma: a report of two cases and review of the literature

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Abstract: Autoimmune diseases (ADs) have close relationship with the onset of malignant lymphoma. They closely tie to lymphoma. Immune disorders might play an important role in transformation from ADs to lymphoma. DLBCL occurred after autoimmune hematological diseases and autoimmune lymphoproliferative syndrome (ALPS) was rare. The interval between ADs and DLBCL was long and the pathogenesis might be related to the immune dysfunction and so on. ALPS might be a bridge. It starts with immune disorders, benign lymphocytic proliferation and infiltration, and at last it progresses malignant histologic variants. We reported two cases of hematological autoimmune disorders developed into DLBCL and ALPS was diagnosed before it evolved into DLBCL. It might help us to predict the risk of lymphoma when the patients are suffered from ADs. New therapeutic methods need to be explored to treat autoimmune hematological diseases. Whether they could prevent ADs from malignant transformation needs further research.

Keywords: Autoimmune diseases, lymphoproliferative syndrome, diffuse large B-cell lymphoma, immune disorders

Introduction

Autoimmune hemolytic anemia (AIHA) and primary immune thrombocytopenia (ITP) are common diseases of the hematopoietic system. But in the chronic courses of the diseases, the occurrences of ALPS and progressions of DLBCL are extremely rare. The pathogeny of DLBCL is not fully understood. AD which acts as a risk factor of DLBCL has been attracting increasing attentions.

Gotschalk and colleagues [1] reported that AD patients had higher risks of suffering from non-Hodgkin lymphoma (NHL). Zintzaras et al. [2] also found that patients with AD and chronic inflammation were at higher risk of NHL. Although malignant lymphoma can often accompany with AIHA, it is infrequent that DLBCL occurs after several years' courses of AIHA. So it is with other autoimmune disorders of hematologic system such as ITP, Evans syndrome and so on. Furthermore, it is extremely rare to be diagnosed with ALPS during the courses of the diseases. In the present study, two cases of DLBCL following hematological autoimmune diseases are reported with a brief review of the literature.

Cases presentation

Case 1

A 55-year-old female patient was admitted to the Third Affiliated Hospital of Peking University (Beijing, China) on November 10, 2010 for the symptoms of pale complexion and weakness. Laboratory results showed that hemoglobin was 53 g/L. The serum total bilirubin was 91.6 μmol/L. The anti-human-globulin test was positive. Doctors made a diagnosis of hemolytic anemia and administrated glucocorticoid. Hemoglobin rose from 35 g/L to 54 g/L. For further treatment the patient was hospitalized to

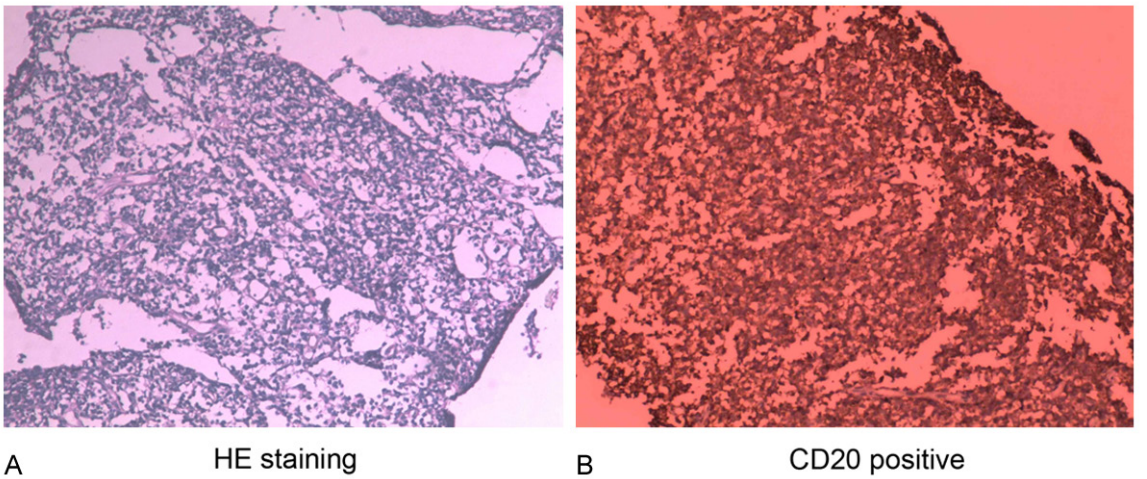

Figure 1. A. Histologic; features; B. Immunohistochemistry of the specimen displaying that the cells were positive for CD20 (Magnification, × 100).

our hospital in November 2010. The invalid was treated with dexamethasone (20 mg/day) and prednisone (55 mg/day) successively. Hemoglobin rose to 115 g/L on April 5, 2011 and glucocorticoid was gradually reduced. The hemoglobin ranged from 102 to 121 g/L. On May 18 of the following year, the patient suffered from cold and felt fatigue, and hemoglobin was 77 g/L and descended progressively. Abdominal ultrasonography displayed a large spleen. The patient refused to use rituximab and she began to take ciclosporin and hemoglobin reached normal. The patient presented to our hospital again on April 19, 2012, with splenomegalia, progressive emaciation and she had lost 7 kg of weight for 4 months and fever for a week. Hemoglobin was 53 g/L. IgM of EB virus was positive. Abdominal ultrasonography displayed a large spleen with the thickness of 8.2 cm and the lasid of 30.0 cm. It was thought to be diagnosed with giant spleen and hypersplenism. She had an operation of splenectomy on May 9, 2012. Histopathological analysis disclosed multifocal coagulative necrosis of spleen and chronic congestion and hyperplastic splenomegaly. Hemoglobin raised little and the anti-human-globulin test was still strongly positive after the surgery. Therefore, the patient was sent to hematology department for further treatment. Bone marrow cytology indicated that the hyperplasia of bone marrow was active. The results of bone marrow biopsy displayed that lymphatic and hematopoietic cell were hyperplastic and lymphocytes occupied the most. Immunohistochemistry showed that CD10 and Bcl-2 were positive, CD3, CD5 and Cyclin D1 were partly positive, and CD20 and Bcl-6 were negative, while Ki67 was lower than 5%. CD3+TCRαβ+CD4-CD8-accounted for 9% in peripheral blood. The enlargement of cervical lymph node existed. Tumor markers were negative. Combined with non-malignantlymphoidenopathy and/or splenomegaly with elevated double negative T-cell count (CD3+TCRαβ+CD4-CD8-≥2.5%) in peripheral blood, the patient was diagnosed as ALPS. Prednisone therapy was commenced and hemoglobin was within normal limits, while the anti-human-globulin test was still strongly positive (4+). Prednisone was reduced gradually and stopped when the liver function test was abnormal in March 2013.

On April 18, 2014, the patient came to our hospital for physical examination and hypoechoic nodules (4.0 × 2.7 cm in the major diameters) were found in the adjacency of the abdominal aorta and the front of left renal hulum on a routine-basis abdominal ultrasonography. Epigastric enhancement CT examination displayed the retroperitoneal multiple lesions: lymphoma? Metastatic tumor? After an abdominal lymph node biopsy guided by ultrasound, a diagnosis of the diffuse large B cell lymphoma (non-GCB) was established. PET/CT indicated that multiple lymphadenopathies at the mediastinum, abdominal cavity and retroperitoneal sites. Collectively, the stage of the disease was con-

sidered as IIIb (**Figure 1**). After two cycles of RCTOD chemotherapy, mediastinal lymph nodes disappeared and retroperitoneal lymph nodes became smaller and hemoglobin was normal and no clinical symptoms were observed, while the anti-globulin test was still strongly positive. The condition of the person is good now.

Case 2

A 48-year-old male patient presented to Southwest Hospital in December 2002 with petechiae and ecchymoses of the whole body after catching a cold. After the examination of bone marrow cytology, she was diagnosed as ITP. Prednisone was administrated and platelet maintained between 30 and 60 × 109/L. The patient adjusted the amount of glucocorticoid by himself. On January 24, 2005, the patient went to the outpatient service and the peripheral blood count showed that leukocyte count and atypical lymphocyte proportion were 12.1 × 109/L and 28% respectively. The indirect anti-human-globulin test was positive (3+). The lymph nodes of bilateral necks, groins and axillas were enlarged and the maximum was 3.3 × 1.52 cm. Infectious mononucleosis was diagnosed and antiviral agents were administrated, and lymph nodes diminished and the percentage of lymphocytes declined sharply.

In June 2005, the laboratory results showed that the atypical lymphocyte proportion was 30%, CD3+CD4+ made up 2.56%, CD3+CD8+ accounted for 1.34%, CD3+CD4+/CD3+CD8+ was 1.91%. The cervical lymph nodes were large and IgM of EBV was weakly positively and tumor markers were negative and ALPS was diagnosed by hematologists in Tianjin institute of hematology. For further treatment, the patient presented to our department on February 13, 2006. Leukocyte count, atypical lymphocyte proportion and platelet count were 21.68 × 109/L, 20% and 86 × 109/L respectively. Abdominal ultrasonography displayed that the thickness was 5.3 cm and the length from the hilum of the spleen to the spleen tip was 9.2 cm. No disease extension to the bone marrow was reported and the IgM of EB virus was still positive. Therefore, chronic EB virus infection was considered and after the administration of antiviral drug, leukocyte count and atypical lymphocyte dropped to normal. From 2008 to 2012 the routine blood tests were basically normal. On January 6, 2013 the patient went to our hospital and the platelet count was 37 × 109/L. The immunophenotyping results of peripheral blood indicated that CD3+/Total, CD3+/CD8+, CD3+/CD4+, CD4/CD8 and CD4+/CD8+/CD2+ were 29.69%, 43.11%, 48.97%, 1.14% and 1.34% respectively. In addition, the parvovirus B19 antibody IgM was suspected and virus infection was considered. Ganciclovir and immunoglobulin were administrated and the blood cells returned to normal.

In February 2013, the invalid developed fever and platelet count was 18 × 109/L. Abdominal ultrasonography showed the thick of spleen was 5.5 cm and the diameter was 18.4 cm from top to bottom and placeholder was not seen. Enlarged lymphnodes were found in neck, axillary and inguinal sites through the examination superficial lymph node ultrasound. Abdominal CT revealed that the spleen occupied nine rib units and the density was uniform. After the administration of antivirus and anti-infection agents, platelet count rose to 38 × 109/L.

In March 2013 the patient suffered from oral herpes. The white cell count and platelet count were 2.56 × 109/L and 10 × 109/L, respectively. The general physical examination revealed that the spleen enlarged. EB virus was negative. The invalid was admitted to liver department for splenectomy. The excised spleen was identified to be spleen lymphatic hematopoietic malignant tumor (large B cell lymphoma) with expressing the CD20, PAX5, CD3, Bcl-2, kappa large cell, ki-67 40% and with no expression of the CD30, CD15, CD21 and EAM. Beijing friendship hospital also made a pathological diagnosis: (spleen) non-Hodgkin B cell lymphoma, high level and the diagnosis was inclined to be follicular lymphoma or nodular large B cell lymphoma. After discussion, a diagnosis of (spleen) diffuse large B cell lymphoma (Phase IIISb) was established (**Figure 2**). Three cycles of R-CTOD therapies were commenced and the superficial lymph nodes significantly diminished and hematopoietic stem cell transplantation (HSCT) was carried out. The condition of the person is good now.

Discussion

Two cases of DLBCL following hematological autoimmune disorders are reported in this article. After their long duration of hematological

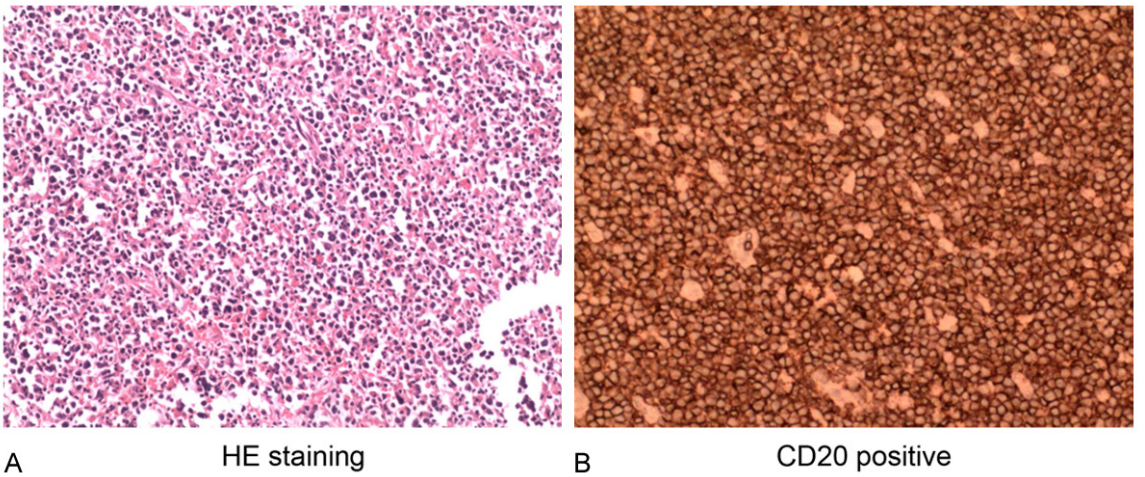

Figure 2. A. Histologic features; B. Immunohistochemistry showed that the cells were positive for CD20 (Magnification, × 100).

autoimmune diseases, ALPS was complicated, and then transformed to DLBCL. The first patient had AIHA for 3.5 years, and she had accepted glucocorticoid and ciclosporin treatment and the effective was partial satisfaction. ALPS was found 1.5 years later after AIHA was diagnosed. The second patient was diagnosed with ITP and he began to administrate glucocorticoid 10 years ago. While the illness attacked repeatedly with varying degrees, and repeated occurrence of EB virus infection. ALPS was found for the first time in 7 years ago. Histopathology and immunohistochemistry verified the diagnosis of DLBCL after a decade of clinical course. These cases illustrate and indicate that the probability of ADs may develop to malignant lymphoma and in which ALPS might play a vital part in the process of canceration.

Autoimmune diseases (ADs) refer to the abnormal activation of the immune system which causes the damage of the own tissues. The main reasons are the appearance of autoantigen, immune dysregulation, cross-reacting antigen, genetic factors and so on. There are more and more reports on systemic ADs complicated by malignant lymphoma, including Sjogren's syndrome (SS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and all of them have correlation with the onset of lymphoma. A follow-up study of 30000 ADs patients showed some NHL were higher risk following ADs, such as marginal zone B-cell lymphoma (MZBCL) and DLBCL. Furthermore, the specific T cell NHL owned high morbidity in coeliac diseases and psoriasis diseases [3].

There exists dual relationship between ADs and lymphoma. Patients with ADs own increased incidence of lymphoma and at the same time lymphoma patients are susceptible to combine with autoimmune phenomena. In the autoimmune hematological diseases, AIHA is an autoimmune disease with abnormal hyperfunction of B lymphocyte, producing its own erythrocyte antibody, increasing the damage of red blood cells and causing anemia. ITP is a common hemorrhagic disease with immune destruction of platelet and thrombocytopenia. It is common to see that lymphoma combines with AIHA or ITP. While AIHA or ITP was confirmed diagnose and a few years later ALPS was suffered and finally it evolved into DLBCL in my case report. There are few reports on ADs developing to malignant lymphoma [4, 5]. The reason is still a mystery. It has not been reported that ALPS involved in the process of transition.

ALPS is a rare and primary immunodeficiency disease and mainly involves in T cells. The disease is caused by Fas mutation which induces apoptosis defects of lymphocytes. The apoptosis pathway mediated by Fas plays a key role in removal of activated T and B lymphocytes and maintaining the homeostasis of lymphocytes. When apoptosis defects happen, cellular and humoral immunity are in disorder, proliferation of lymphocytes happens and abnormal lymphocyte subsets increased. Fas gene mutation blocks apoptosis and induces the release of growth factors or induces excessive proliferation of lymphocytes. And the above might boost the growth of tumors especially lymphoma.

ALPS is common to see in children. Our report showed that it could also occur in adults. More than 80% of ALPS patients own autoantibodies which can exist for several years before the onset of disease. Direct anti-globulin test and anti-granulocyte antibodies are positive, and anti-granulocyte antibodies, anti-cardiolipin antibodies, anti-nuclear antibodies and rheumatoid factor (RF) can also be positive. There are some correlation between the titer of antibodies and the number of the double negative T cells (DNTs). Continuous proliferation of lymphocytes is the most common clinical manifestation of ALPS, and ADs is another common clinical feature.

What is the mechanism of DLBCL following ADs of blood system? AS we know, under normal circumstances, T and B lymphocytes respond to an antigen and cause self-limited proliferation. But in the state of ADs, function abnormality of immunocytes occurs, such as apoptosis resistance, impaired function of T and B cells and cause the onset of malignant lymphoma [6]. Fas receptor and FasL ligand are the main factors affecting the apoptosis of T cells [7]. The apoptosis defects of T cells induces the abnormal proliferation of B cells. Gene mutation exists in approximately 70% of patients with ALPS, and almost all mutations are involved in the Fas mediated apoptotic gene [8]. The pathogenesis of ALPS lies in the lack of apoptosis of activated T immune cells [9]. The patients in our report suffered from AIHA and ITP respectively, and then the continuous stimulation of self antigen caused the gene mutation of Fas receptor and Fas ligand and inhibition of immune cells apoptosis, and eventually led to ALPS.

It was reported that ALPS cells had apoptosis defect, the incidence of malignant tumors was really high [10]. ALPS patients have 14 times high risk of developed NHL than expected [11]. In my report, both of the patients were diagnosed with ALPS and the diseases eventually evolved into DLBCL.

In the same time, immunosuppressive therapies can also make immune dysfunction of the bodies and abnormal immune regulation, which may weaken the immune surveillance function and at the same time may attenuate the immune inhibiting abilities of malignant cells and cancer-causing virus infection. Abnormal lymphocytes proliferate without limitation and eventually lead to lymphoma [12]. Studies have reported that glucocorticoids were associated with the increase of NHL [13]. Moreover, we can assume that there exists co-susceptible gene between some blood system ADs and NHL. To test this hypothesis, Ekstrom and colleagues [14] reported that family history of RA patients was generally not a predictor of lymphoma risk. Further research is needed.

EBV is an oncogenic virus and it has been proven to be related to certain types of lymphoma. The dysfunction of T cell is a major risk of lymphoma which can promote EBV replication. EBV infection is more common in immunosuppressed NHL patients compared with NHL patients with normal immune systems [15]. Studies indicated the EBV levels were a slightly higher in RA-related lymphomas compared with in non-RA-related lymphomas [16]. Therefore, EBV may be an etiological factor of RA-related lymphoma, while the roles in other ADs especially ADs of blood system need further study. Both of the patients in my report were also infected with EBV which might contribute to the onset of lymphoma.

B cell activating factor (BAFF) has close relationship with the growth and survival of B cell malignant tumors. BAFF has a vital role in regulating B lymphocytes proliferation and differentiation. BAFF is closely related to the pathogenesis of ADs, ALPS and B-NHL. The serum BAFF levels are higher in SS, RA, SLE, ALPS and lymphoma patients compared with those of normal humans [17-20]. BAFF might play a vital role in the malignant transformation from ADs to ALPS and tumors. BAFF can induce the produce of Bcl-2 family proteins such as Bcl-2, Mcl-1 and Bcl-XL and protect tumor cells from apoptosis [18-23]. Therefore, targeting BAFF may provide a new therapeutic strategy for patients with lymphoma, ALPS and ADs.

Little attention has been paid on the treatment of ADs concurrently or secondary to DLBCL. Clinicians mainly adopt the regimens of antitumor treatment and symptomatic treatment at the same time. Glucocorticoid, immunoglobulin, mycophenolate mofetil and rituximab are currently used for the treatment of AIHA, ITP and ALPS. Rituximab has been recommended as the treatment of autoimmune disorders in recent years. Aarati et al. [19] reported 30

cases of children with refractory hematologic autoimmune cytopenias received the therapy of rituximab and the overall response rate was 72%, including 69.5% of ITP and 62.5% of AIHA. In another study of adult ITP patients, the overall response rate was 54% [20]. The high response rate and good tolerance make rituximab be a better therapy compared with consideration of intense immunosuppression or splenectomy to treat the refractory or persistent autoimmune hematologic cytopenias. Autologous transplantation is the only way to cure ALPS. If the patient owns Fas gene mutation, his family members have high morbidity to suffer from ALPS concurrent with lymphoma. Genetic tests and close follow-up need to be conducted. Thoracic, abdominal and pelvic CT scan should be done periodically to evaluate the diseases.

ALPS patients with lymphoma have poor response to traditional chemotherapeutic agents. R-CHOP therapy has become the standard treatment of DLBCL [21, 22]. Rituximab was used in CD20 positive NHL patients and many clinical data confirmed the curative effect [23]. So it was with recurrence or drug-resistant cases [24]. Hence, rituximab can kill two birds with one stone. In addition, about 20% of patients with R-CHOP regimen still can not achieve complete remission (CR) and the patients need other treatments. As to the prognosis of lymphoma following ADs, there are little data to make calculation and more research needs to conduct.

Clinicians administrate immune adjustment or immunosuppressive therapy to the patients with autoimmune diseases. These treatments can directly cause the susceptible gene mutation, reduced immune surveillance, abnormal proliferation of B cells which contribute to the onset of NHL. In clinic, we should think of the possibility of concurrent or secondary to lymphoma for the patients with ADs of hematologic system, especially those patients with high risk factors. We should take effective method, select appropriate intervention to reduce risk factors. Patients with ALPS should be regularly monitored to prevent the progress of the diseases. FDG-PET/CT might act a significant part in it [25]. Rituximab and targeting BAFF have extensive application prospects in patients with ADs and lymphoma. HSCT is the only way to cure lymphoma and its application in ADs is more and more widely. Farge et al. [26] reported 900 severe AD patients received ASCT, the 5-year survival was 85% and progression-free survival was 43%. Therefore, ASCT may be an effective method in treating patients with severe ADs. The cause, specific pathogenesis, the pathological and physiological changes of the transformation from ADs to lymphoma have not been elucidated and require further research. The identification and function studies of these susceptibility genes will help invalids with early warning early screening and early treatment.

Conclusion

ADs have close relationship with malignant lymphoma and immune disorders and ALPS might play a key role in it.

Disclosure of conflict of interest

None.

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