Autoimmune hemolytic anemia as presenting manifestation of primary splenic anaplastic large cell lymphoma

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Autoimmune hemolytic anemia (AIHA) is an unusual complication of malignancy. We diagnosed primary splenic anaplastic large cell lymphoma (ALCL) in a patient. A seven-year-old boy presented with Coombs test-positive hemolytic anemia. After a course of prednisolone therapy, a complete response for anemia was achieved. Twenty months later, in addition to severe hemolytic anemia, the patient was diagnosed with ALCL after splenectomy and pathologic examination of the sample. The recognition of this clinical picture as a complication of non-Hodgkin’s lymphoma has important implications. The most effective management of AIHA in the setting of cancer is to treat the underlying malignancy.

Key words: autoimmune hemolytic anemia, anaplastic large cell lymphoma, spleen, non-Hodgkin’s lymphoma, childhood.

Various immunologic abnormalities such as autoimmune hemolytic anemia (AIHA), immune thrombocytopenic purpura, and immune neutropenia have been described in patients with malignancy¹-³. AIHA is the most common of these complications, occurring in approximately 2-3% of patients with non-Hodgkin’s lymphoma⁴,⁵. The spleen is often involved in disseminated non-Hodgkin’s lymphoma, but primary splenic lymphoma is extremely rare. We present the case of a child with AIHA and splenic anaplastic large cell lymphoma (ALCL).

Case Report
A seven-year-old boy was admitted to our hospital with a 20-day history of jaundice, fatigue and paleness. He had no signs of infection and was not taking any medicine. His family had no similar illness. His physical examination revealed pallor, jaundice and minimal hepatosplenomegaly. There was no lymphadenopathy. The peripheral blood count showed a hemoglobin level of 4 g/dl, hematocrit value of 10.8%, platelet count of 237,000/mm³ and a white blood cell count of 8,300/mm³ with a normal differential. The peripheral blood smear revealed severe anisocytosis, spherocytosis, poikilocytosis and polychromasia of the red blood cells. The reticulocyte count was 10%. The erythrocyte sedimentation rate was 97 mm/h. The direct Coombs test was positive for IgG. The serum chemistries were normal except for slightly elevated indirect bilirubin and lactate dehydrogenase levels. The antinuclear antibody titer was negative. The serum immunoglobulins, and C3 and C4 levels were normal. The boy’s antibody titers for cytomegalovirus (CMV) and Epstein-Barr virus (EBV) suggested a past infection. Human immunodeficiency virus (HIV) was negative serologically. The patient was given a course of high-dose methylprednisolone therapy (30 mg/kg daily for 3 days and then 20 mg/kg daily for 4 days). After the steroid was administered to the patient, the hemoglobin level increased, direct Coombs test became negative, and the number of reticulocytes decreased. Organomegaly of the liver and spleen was resolved. The patient visited our clinic for regular check ups and his AIHA was in remission.
However, 20 months later, he returned to our clinic because his problems had reappeared. On physical examination, pallor, jaundice, and minimal splenomegaly were observed. There was no lymphadenopathy. The peripheral blood count showed a hemoglobin level of 6.4 g/dl, hematocrit value of 19.6%, platelet count of 336,000/mm³ and a white blood cell count of 10,300/mm³ with a normal differential. Abdominal ultrasound revealed splenomegaly but no lymphadenopathy was determined. He was determined to have relapsed. A steroid therapy was administered to the patient again, and his status improved considerably. Despite glucocorticoid therapy, the Coombs test remained positive and no decrease in the sedimentation was observed. The steroid was given at the minimum dose every other day to reduce the side effects. It was observed that he was uninterested in his surroundings and apathetic. During this episode, his serum glucose level was 300 mg/dl, and his blood pressure was 150/100 mm Hg. The steroid was discontinued, as it was considered to cause side effects, by administering single-dose ACTH. After the steroid was ceased, his complaints resolved. He relapsed when steroid dosage was lowered. Intravenous immunoglobulin G (IVIG) therapy was planned but it could not be administered. Thus, splenectomy was performed, taking the necessary precautions. No pathologic lymphadenopathy or mass in the abdomen was seen during the exploration. The histopathologic examination revealed multiple foci of tumoral infiltration. The neoplasm was highly cellular, composed of large mononuclear cells with pleomorphic nuclei containing nucleoli and little cytoplasm. In the immunohistochemical studies, CD30 and CD3 tests were positive, and CD15, CD20 and CD23 tests were negative. Immunostaining for ALK could not be performed. Therefore, a diagnosis of anaplastic large cell of T-cell type was made. The abdomen ultrasound examination, and abdomen and chest computed tomography were normal. Bone marrow aspiration and cerebrospinal fluid examination were normal. He had stage III disease according to Murphy’s staging system. Therefore, primary splenic ALCL was diagnosed and the LSA2-L2 chemotherapy regimen was started. After therapy, his hemoglobin level, reticulocyte count and erythrocyte sedimentation rate were normal and the direct Coombs test was negative. The patient was able to successfully complete chemotherapy. He is still under follow-up and is disease-free five years after the diagnosis.

Discussion

In AIHA, abnormal antibodies directed against red blood cells are produced by the patient. Autoimmune hemolytic anemias associated with an underlying disease process such as lymphoma, lupus erythematosus or immunodeficiency are said to be secondary or symptomatic. Autoimmune hemolytic anemias occur in two general clinical patterns. The first is an acute transient type that occurs predominantly in infants and younger children. It is frequently preceded by an infection. A consistent response to corticosteroid therapy and full recovery within three months are characteristic of the acute form. The second type pursues a prolonged and chronic course. The response to corticosteroids is variable and inconsistent. Immunosuppressive agents have been of some benefit in chronic cases refractory to conventional therapy. If severe chronic hemolysis continues, splenectomy should be considered.

In our case, idiopathic AIHA was diagnosed. We treated our case successfully with corticosteroids, and the patient stayed in remission for 20 months, after which he experienced a second relapse. We tried to treat the second relapse with corticosteroid, but the drug had to be discontinued because of the side effects. We were not able to supply IVIG; therefore, splenectomy was preferred for the treatment of AIHA.

An association between autoimmune phenomena and non-Hodgkin’s lymphoma is well known. Its incidence is reported to be 13.7%. The incidence of AIHA in patients with non-Hodgkin’s lymphoma is 2-3%. It can rarely occur one or two years later. In addition, the appearance of this complication seemed to be independent of the stage of disease, and patients with non-Hodgkin’s lymphoma who did not develop AIHA had better overall survival compared to those with non-Hodgkin’s lymphoma who developed AIHA. A minimum tumor load of lymphoma undetectable by the usual investigations may be associated with AIHA. It can help us to determine lymphoma relapse. 

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The mechanism by which patients with cancer develop AIHA is speculative. AIHA pathogenesis in the lymphoma is still an issue of discussion. The most effective management of AIHA in the setting of cancer is to treat the underlying malignancy. The therapy resolved the hemolysis4,5,9.

Splenic involvement can be part of a diffuse dissemination of non-Hodgkin’s lymphoma in which the spleen is one of multiple involved organs or sites. However, primary splenic lymphoma is a rare entity. For the diagnosis of primary splenic lymphoma, strict criteria have been defined. Primary splenic lymphoma may only be diagnosed if the spleen and splenic hilar nodes but no other organs show neoplastic infiltrates11. Brox et al.12 reported that 0.57% of patients with non-Hodgkin’s lymphoma were identified with lymphoma localized solely in the spleen or extended to the splenic hilar nodes. The most common symptom is abdominal pain in the left upper quadrant12,13.

Anaplastic large cell lymphoma is defined by a neoplastic proliferation of large, atypical lymphoid cells displaying anaplastic nuclear morphology and expressing the activation marker of CD30 in over 70% of its cells. It has a predilection for the lymph nodes and skin.

Splenic involvement of ALCL is rare for this particular lymphoma14-16. In the literature, several cases have been reported14-17. Hansmann et al.14 reported a 50-year-old man presenting with splenomegaly. Lymphoma cells were of the B-cell type CD30 positive. In the case described by Bellamy et al.15, lymphoma of the spleen was associated with HIV infection and the tumor cells expressed EBV-associated antigens. Nai et al.16 reported that their patient had chronic lymphocytic leukemia (CLL) and according to these authors the development of these lymphoma could represent a case of Richter’s syndrome. Sakadamis et al.17 reported a 62-year-old woman presenting symptoms resembling a splenic abscess.

In our case, after splenectomy, CD30 positive primary splenic ALCL was diagnosed based on the histopathologic examination and investigative studies.

In conclusion, this is the first report of pediatric primary splenic ALCL presenting with AIHA in the literature. Patients diagnosed with AIHA should be observed carefully over a long time, and the presence of an underlying disease should be investigated, especially in chronic cases.

REFERENCES