

Autoimmune Hemolytic Anemia Revealing Classical Hodgkin Lymphoma: Two Case Reports and Literature Review

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Abstract

Background: Hodgkin Lymphoma (HL) is rarely associated with autoimmune hemolytic anemia. We report here two cases of such association: Case 1: 57 years old man who presented with tiredness and pallor. Physical examination revealed multiple left cervical lymph nodes. Blood count showed regenerative macrocytic anemia with signs of hemolysis. Auto immune hemolytic anemia was confirmed by a positive direct antiglobulin test for IgG and C3d; lymph node biopsy revealed lymphocytic rich HL. Case 2: a 50 year old man being treated for HL for few months

presented to the emergency room for dyspnea and pallor. Blood count showed regenerative macrocytic anemia with positive direct antiglobulin test for IgG and C3d confirming the diagnosis of AIHA as a relapse of the lymphoma. These two cases show that clinicians should be aware of such association revealing the diagnosis or the relapse of the lymphoma to distinguish it from anemia of chronic disease.

Keywords: Hodgkin lymphoma; Auto immune hemolytic anemia; Macrocytic anemia

Introduction

Hodgkin Lymphoma (HL) is a monoclonal B-cell neoplasm presenting typically with painless lymph nodes often affecting the cervical chain. Other nodal sites may be affected, but extra nodal localizations are less common.¹

Auto immune hemolytic anemia (AIHA) is an acquired clinical condition which is characterized by the production of auto-antibodies that bind to the surface of circulating erythrocytes, leading to hemolysis and decreased survival of the red blood cells.² Fifty four percent of AIHA cases in adults are secondary to underlying causes such as autoimmune diseases and malignancy.³ It may occur in lymphoproliferative diseases, especially chronic lymphocytic leukaemia (CLL) and to lesser extent non Hodgkin lymphoma. Unlike the other lymphoproliferative diseases, HL is rarely associated with AIHA.² In this report, we describe two cases of associated AIHA with HL revealing the disease in one case and showing relapse in the other case.

Case 1

A 50-year old man was admitted in the internal medicine department in 2011 to assess redundant-disseminated lymphadenopathy. A cervical node was biopsied revealing Hodgkin lymphoma with mixed cellularity

subtype, testing positive for CD15 and CD 30 positivity on immunohistochemistry. The body scan showed superior and inferior diaphragmatic lymph node involvement with pulmonary parenchymal involvement. The HL was diagnosed stage IIIB based on Ann Arbor classification and treatment with BEACOPP chemotherapy was started (Bleomycin 10mg/m², Etoposide 100 mg/m², Doxorubicin 35 mg/m², Cyclophosphamide 1200 mg/m², Vincristine 1.4mg/m², Procarbazine 100 mg, Prednisone 40 mg/m², all of them day 1 and day 8). After eight cycles the patient presented to the emergency room with dyspnea and marked pallor. A full blood count showed a regenerative macrocytic anemia with Hemoglobin (Hb) = 3.9 g/dl and mean corpuscular volume (MCV) = 111 fl. Reticulocyte count was 220 000 elements/mm³ (Elt/mm³), white blood cells (WBC) were at 1030 elt/mm³, neutrophils at 500 and lymphocytes at 500 elt/mm³. Direct antiglobulin test (DAT) at 37°C was strongly positive for IgG and C3d. The diagnosis of AIHA was made reflecting a relapse of the disease. High doses of prednisone were started at 1mg/kg body weight with a good response, followed then by chemotherapy with the ABVD regimen: Doxorubicin 25mg/m², Bleomycin 15 mg, Vinblastine 10 mg, Dacarbazine 375 mg/m². A total of four cycles of chemotherapy were given. Two weeks after, the patient presented with a severe sepsis secondary to chemotherapy refractory to treatment and died.

Case 2

A 57 year-old male presented to the internal medicine department in 2014 with the history of general malaise, tiredness, night sweats and fever. Clinical examination revealed marked pallor with moderate jaundice, icteric conjunctivae and tachycardia associated with painless

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left magma of cervical lymph nodes. There was no hepatosplenomegaly and no edema of the extremities. A full blood count showed a regenerative macrocytic anemia with Hemoglobin (Hb) = 5.7g/dl and mean corpuscular volume (MCV) = 108.9 fl. Reticulocyte count was 387 000 elements/mm³ (Elt/mm³), white blood cells (WBC) were at 8030 elt/mm³, neutrophils at 5800 and lymphocytes at 1600 elt/mm³. Direct antiglobulin test (DAT) at 37°C was strongly positive for IgG and C3d. Blood biochemistry showed normal urea, creatinine and electrolytes. Bilirubin was raised at 30.4 µmol/l with elevated indirect bilirubin and serum LDH at 226U/l.

A fine needle aspiration of the lymph node showed an aspect of Hodgkin lymphoma confirmed by a biopsy showing Reed-sternberg cells with CD30, CD15 and CD20 positivity on immunohistochemistry (Figure 1, 2 and 3). A whole body CT scan showed the absence of liver or spleen involvement as well as inferior diaphragmatic lymphadenopathy.

A diagnosis of warm antibody type auto immune hemolytic anemia associated with Hodgkin lymphoma in its lymphocytic rich form was made. He was initially started on prednisone 1.0mg/kg body weight followed by chemotherapy with the ABVD regimen: Doxorubicin 25mg/m², Bleomycin 15 mg, Vinblastine 10 mg, Dacarbazine 375 mg/m². A total of four cycles of chemotherapy were given. After all of that radiotherapy was given. Currently, one year after laboratory results are normal and the patient is in remission.

Discussion

Hodgkin lymphoma (HL) is a malignant disorder of the lymphatic system which is more common in males.¹ Its incidence peaks at two age spans: between 15-35 years and older than 55 years.¹ Patients usually have painless lymphadenopathy at initial presentation. Extralymphatic tissue involvement is rare.¹ The diagnosis of HL requires an expert hematopathologic interpretation of a lymph node specimen. Presently, HL is classified into two largely distinct entities, namely nodular lymphocyte-predominant HL (NLPHL) and classical HL (CHL), the latter being further subtyped as nodular sclerosis (NSCHL), lymphocyte-rich (LRCHL), mixed cellularity (MCCHL), and lymphocyte-depleted (LDCHL) subtype.² LRCHL has an excellent prognosis, with event-free and overall survival rates of 97% at 30 months.²

AIHA can be associated with autoimmune diseases or malignancies. It is rarely seen in Hodgkin lymphoma.⁴ Such association was first reported in 1966 by Bowdell and Glick in a man aged 18 years with AIHA 36 months before the diagnoses of a stage III HL.⁵ The reported incidence of AIHA in HL is 0.2 -4.2%^{6,7} making it one of the more common of the unusual paraneoplastic manifestations of this disorder.

Qi Feng et al., reviewed 39 published cases, including eight pediatric, of HL with AIHA. 93% patients had a positive direct Coombs test, mostly specified as IgG and/or C3 (57%).

Among 29 cases with reported pathologic subtypes, 14 (48%) had MCHL, 10 (34%) had NSHL, three (10%) had LRHL, one (3.0%) had both MCHL and NSHL, and one (3.0%) fell between NSHL and the lymphocyte-depleted subtypes.¹ This observation supports the theory that AIHA can occur in all subtypes of HL. The fact that AIHA was found more often in the MCHL and NSHL subtypes than in the LDHL or LRHL subtypes may be because the first two subtypes are more common.¹ According to Q Feng et al, AIHA was the onset symptom of HL in 16 (40%) patients, but it preceded HL by eight to 36 months in eight (20%) patients.¹

The biologic explanation for the AIHA frequency in lymphoid malignancy is complex and not completely understood. Different mechanisms may be involved, such as antigen presentation by neoplastic cells, loss of tolerance induced cytokines release and auto-antibodies secretion.⁹

To treat AIHA associated with lymphoid malignancy corticosteroids are the mainstay of therapy associated with immunosuppressive drugs such cyclophosphamide or antitumoral chemotherapy.¹⁰⁻¹² IVIg may induce a short term response.¹¹⁻¹² In the first case, despite the good response to the AIHA treatment, the patient died because of infectious complications of chemotherapy.

In the second case, our patient had a rapid and sustained response to oral steroid therapy. His clinical course improved without further need for packed red blood cell transfusions with an increase in hemoglobin concentration as well as decreased reticulocyte counts and serum lactate dehydrogenase levels. When the diagnosis of HL was confirmed, combined chemotherapy against HL was delivered.

Conclusion

AIHA is rarely associated with HL. It can reveal the disease or complicate its course. Clinicians should be aware of such association which can reflect a relapse of the disease and distinguish it from the anemia of chronic disease.

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