Autoimmune Hemolytic Anaemia in Hodgkin's Lymphoma

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Abstract
Autoimmune hemolytic anaemia is a rare presentation of Hodgkin’s lymphoma though its association with Non- Hodgkin’s lymphoma is well known. It is usually detected at the time of diagnosis when it accompanies Hodgkin’s and rarely precedes it. It is a warm immune hemolytic anemia which is responsive to steroids and rituximab. We hereby report a case of advanced Hodgkin’s disease who presented as AIHA.

Introduction
Autoimmune hemolytic anaemia is an uncommon disease. The estimated overall annual incidence is about 1 case per 100,000 in the population. AIHA is a recognized complication of lymphoproliferative disorders. Association of AIHA with Hodgkin’s lymphoma is very rare ranging from 0.2% in a large series of 492 patients from Europe to 3-4% in American studies. This association was first described by Eisner et al in 1967.

Hodgkin’s lymphoma is phenotypically classified as Lymphocyte predominant and Classical Hodgkin’s. The latter is characterized by heterogeneity and architectural effacement on histopathology. Classical Hodgkin’s is CD30 positive and occasionally positive for CD20 and CD15.

Hodgkin’s lymphoma is usually manifested as lymphadenopathy typically in the cervical (70%), axillary (25%), mediastinal areas (60%), and in 16-34% of the cases, presents as nodal disease below the diaphragm. Hodgkin’s lymphoma presenting as AIHA has been reported in very few case reports in literature. We hereby report a case of advanced Hodgkin’s lymphoma who presented as AIHA.

Case Report
A 42 years old male with diabetes since 15 years presented with on and off fever, generalized weakness and yellowish discoloration of urine of one month duration. His urine subsequently became dark brown in colour. There was no other significant history other than an episode of jaundice 2 years back. On examination his vital parameters were stable. He had icterus, right supraclavicular non tender, firm lymph node of 1.5 x 2 cm size and bilateral pedal oedema on general examination. Systemic examination revealed Hepatosplenomegaly and Bilateral basal crepitations.

His investigations revealed unconjugated hyperbilirubinemia with Total Bilirubin- 6.1mg/dl and Direct Bilirubin- 2.8 mg/dl) and Coombs positivity with Peripheral smear evidence of spherocytes suggestive of Immune hemolytic anemia. His serum Creatinine was 1.7 mg/dl suggestive of acute kidney injury possibly due to hemoglobinuria, as suggested by his dark brown urine which subsequently improved. His ultrasound abdomen showed paraaortic lymphnodes with mild hepatosplenomegaly and mediastinal widening was seen on his chest radiography. CT thorax showed pretracheal, aortopulmonary and retrocaval lymph nodes. His lymph node biopsy showed Reed Sternberg cells. A diagnosis of autoimmune hemolytic anemia with ? Mediastinal NHl ? Hodgkin’s lymphoma was made. Immunohistochemistry revealed CD 30 positivity and occasionally CD20 positive suggestive of Hodskins lymphoma (Classic type). CD 15 and ALK(anaplastic lymphoma kinase) were negative. Bone marrow examination revealed reactive hyperplasia. Our patient had stage III disease with ‘B’ symptoms.

Patient improved symptomatically on treatment with steroids, brownish discolouration of urine disappeared. Patient was started on chemotherapy cycles with inj Adriamycin, inj Bleomycin, inj Vinblastine, inj Dacarbazine and inj dexamethasone at referral oncology centre.

Discussion
Autoimmune hemolytic anemia occurs when a patient produces pathologic antibodies that attach to and lead to the destruction of red blood cells causing anaemia. Warm antibodies are typically of the IgG variety, may or may not fix complement, and primarily lead to RBC loss by splenic removal of sensitized cells. Acquired AIHA has been described to be associated with an underlying disease in more than fifty percent of cases. AIHA is a recognized complication of lymphoproliferative disorders, especially Chronic lymphocytic leukemia and Non Hodgkin’s lymphoma. It is uncommon in Hodgkin’s disease. The characteristic finding in bone marrow in AIHA is erythroid hyperplasia which was also seen in our patient. However, examination of marrow is needed only if there are unexpected findings or suspicion of a lymphoma. When Hodgkin’s is accompanied by AIHA, the haemolysis is usually detected at the time of diagnosis or a relapse. In a rare scenario it has been reported to precede the diagnosis of Hodgkin’s, in one case by up to 7 years. In majority of these patients, AIHA is associated with clinical or pathological evidence of stage III or IV disease. The exact mechanism of AIHA in Hodgkin’s is still unclear. However it may be postulated that the autoantibodies are directly produced by tumour cells or are related to an immune regulatory phenomenon or as a paraneoplastic process. Treatment with anti CD20 antibody rituximab, which suppresses the B-lymphocytes, has shown to be effective in idiopathic AIHA. Although the initial treatment of AIHA is steroids, immune haemolysis associated with Hodgkin’s requires definitive treatment with systemic chemotherapy.

Approximately 25% of patients with Hodgkin’s lymphoma have constitutional symptoms which were seen in our patient. Because Hodgkin’s lymphoma can involve the bone marrow
extensively, an occasional patient has symptomatic anaemia or incidentally noted pancytopenia. The diagnosis of Hodgkin’s lymphoma is based on recognition of Reed-Sternberg cells or Hodgkin’s cells (or both) in an appropriate cellular background in tissue sections from a lymph node or extra-lymphatic organ, such as bone marrow, lung, or bone. In Classic Hodgkin’s lymphoma, scattered large Reed-Sternberg cells (RS) are either multinucleated or have a large polypliod nucleus. RS cells alone are insufficient to establish the diagnosis. The immunophenotype of the neoplastic cells in Hodgkin’s lymphoma can help identify the specific subtype.

Typically, the Hodgkin/Reed-Sternberg cells stain positively for CD30 (80-100% of cases), CD15 (75-85% of cases), and B-cell–specific activating protein (BSAP), which is the product of the PAX5 gene (>90% of cases). CD20, a generally reliable marker of B-cell lineage, is positive in about 40% of cases of classic Hodgkin’s lymphoma but the staining can be weak. In contrast, Nodular Lymphocyte-predominant Hodgkin’s lymphoma almost always stains strongly positive for CD20 and for the specialized B-cell markers CD79a and CD45, but it is negative for CD30 and CD15. Finally, anaplastic large cell lymphoma is reliably negative for CD15, CD20, and CD79a but frequently positive for anaplastic lymphoma kinase (ALK). T cell rich B-cell lymphoma is distinguished from Classic Hodgkin’s lymphoma by being CD30 and CD15 negative but positive for CD20 and CD45.

Glucocorticoids at 1-1.5mg/kg dose are the initial therapy of choice for warm AIHA. Response may not be evident for 3-4 days but noticeable by 7 days. Dose reduction has to be attempted after six weeks and slow tapering to be continued for three months. ABO typing of patient’s blood is not problematic with warm autoantibodies. Other treatment options in unresponsive patients include splenectomy, anti-mitotics and anti-metabolites.

Our report illustrates that patients with AIHA should be regularly and carefully monitored for manifestations of a concomitant disease, such as Hodgkin’s disease, developing later.

References