

## **Case Report**

# **Autoimmune Haemolytic Anaemia preceding the diagnosis of Hodgkin's Disease: A report of two cases and review of the literature**

Neelam Siddiqui, Aamer Aleem

The Department of Medicine, Haematology/Oncology Division, College of Medicine & King Khalid University Hospital, Riyadh, Saudi Arabia.

### **Abstract**

Autoimmune haemolytic anaemia (AIHA) is known to be associated with Hodgkin's disease (HD) but is uncommon. It usually presents at the time of initial diagnosis of HD or during the course of the disease but AIHA preceding the diagnosis of HD is very rare. We describe here 2 cases of AIHA who presented one year before the diagnosis of HD. There was no evidence of a coexisting disease at initial diagnosis. Both of the patients required steroids throughout this period to control AIHA. Our report illustrates that patients with AIHA should be regularly and carefully monitored, particularly in treatment resistant cases, for manifestations of a concomitant disease, such as HD, developing later.

### **Introduction**

Hodgkin's disease (HD) classically presents with lymph node enlargement with or without 'B' symptoms (Unexplained weight loss exceeding 10% of body weight in 6 months, fever and drenching night sweats). Anaemia is a common manifestation of Hodgkin's disease and different mechanisms which contribute to anaemia include anaemia of chronic disease, reduced red cell survival, bone marrow infiltration, autoimmune haemolytic anaemia (AIHA) and bone marrow suppression by chemotherapy. AIHA associated with HD is uncommon.<sup>1</sup> The diagnosis of AIHA is usually associated with HD at the time of initial presentation or during the course of disease, but not preceding it.<sup>2,3</sup> We describe here two patients who were diagnosed to have AIHA one year preceding the development of stage IV and stage III, mixed-cellularity type HD respectively.

### **Case 1:**

A 32-year old male presented with a history of malaise, intermittent fever and dizziness with yellow discolouration of the sclera and dark urine of one month duration. There was no antecedent history of viral type illness or anaemia. Clinical examination revealed an ill looking man with marked pallor and mild icterus. He was febrile with a temperature of 38°C. Rest of the examination was unremarkable. In particular there was no hepatosplenomegaly or lymphadenopathy (LAP). Laboratory investigations showed haemoglobin of 49g/l, Haematocrit value 15%, MCV 118.8 fl, MCH 38pg and

reticulocytes 16.2%. The white blood cell count was  $7.8 \times 10^9/l$  with 44% lymphocytes, 49% neutrophils, monocytes 6%, basophils 1%. Liver function tests indicated indirect hyperbilirubinaemia and the lactate dehydrogenase (LDH) was elevated at 527 u/l (NR 100-190). A direct and indirect Coomb's test was strongly positive for IgG + C<sub>3</sub>. The platelet count, G-6-PD screen and haemoglobin electrophoresis were all normal. Viral serology, tests for cold agglutinins as well as rheumatoid factor, anti nuclear antibodies, malaria screen and HIV were negative.

An exhaustive search for coexisting malignancy especially lymphoproliferative disorders was made. A bone marrow examination showed hypercellular bone marrow with erythroid hyperplasia; eosinophils were numerically increased (4.1%) and lymphocytes were normal. There was no evidence of a malignant tumour or granuloma formation. Chest x-ray was normal, CT scan of the abdomen showed a mildly enlarged spleen and a normal liver with no focal lesions. There was no LAP.

A diagnosis of idiopathic AIHA was made. Prednisolone 60 mg and folic acid 5 mg was administered daily and the patient was discharged on tapering doses of prednisolone. In one month his haematological and biochemical parameters had normalized. Following that the patient failed to attend for his clinic appointment. However, he continued to self administer steroids intermittently. Exactly one year after his first admission, he presented with a history of fever, malaise and right upper quadrant abdominal pain of ten days duration. On examination he was found to have hepatosplenomegaly. The liver was firm and non tender, 9 cm. below the costal margin and spleen tip could be palpated. There were no palpable lymph nodes. Haemogram revealed haemoglobin of 109g/l, normocytic normochromic picture, white cell count of  $10 \times 10^9/l$ , 54% lymphocytes, 25% neutrophils, 6% monocytes, 6% eosinophils, 3% basophils, atypical cells 5%, bands 1% and ESR was 62mm/hr.

Direct and indirect Coombs' test was positive. Liver function tests showed normal bilirubin with elevated alkaline phosphatase at 780 u/l (Normal range [NR] 50-136 u/l), gamma-glutamyltransferase (GGT) 478 u/l (NR 15-85 u/l), alanine transaminase 79 u/l (NR 20-65 u/l) and aspartate transaminase 57 (NR 13-37 u/l). On CT scan of the abdomen, there was hepatosplenomegaly with multiple hypodense

lesions scattered throughout both liver and spleen. There were enlarged para-aortic lymph nodes as well. A tru-cut biopsy of the abdominal lymph node as well as a biopsy of the hepatic lesion revealed mixed cellularity Hodgkin's disease. This was consistent with a diagnosis of stage IV-B, HD. Subsequently the patient received 8 cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy. Post treatment CT scans showed complete resolution of the disease. Repeat haemoglobin, red blood cells indices and peripheral blood smear were all normal. Markers of haemolysis indicated remission of AIHA.

### Case 2:

A 44 year old male patient was referred from a peripheral hospital with a 3 month history of increasing fatigueability and shortness of breath on exertion. Eight weeks before presentation he developed yellowness of eyes and skin. There were no other symptoms and there was no history of drug intake. Examination showed pallor, jaundice and splenomegaly. Investigations revealed low Hb (41g/l), raised MCV (127 fl), high reticulocyte count (30%), raised LDH (721 u/l), high total bilirubin (46.5  $\mu$ mol/l) and indirect bilirubin (26.3  $\mu$ mol/l). A direct and indirect Coomb's test was strongly positive both for IgG and C<sub>3</sub>. Other investigations including autoimmune screen, chest x-ray and US abdomen were all normal. He was diagnosed to have idiopathic AIHA. He received blood transfusion and was started on steroids without a good response. At this stage he received intravenous immunoglobulin (IV IgG) and was started on danazol. As there was no haematologist available to take care of him, he was referred to our centre.

He was seen at our center 3 months after the initial diagnosis. He complained of mild shortness of breath and fatigue of 2 weeks duration. He was receiving prednisolone 10 mg daily along with danazol and folic acid. Examination revealed mild pallor and a just palpable spleen. Laboratory workup showed low Hb (112 g/l) with a normal WBC and platelet count. Reticulocyte count was mildly raised (2.7%) and peripheral blood film showed polychromasia and few spherocytes. A direct Coomb's test was strongly positive. Serum biochemistry revealed normal total and indirect bilirubin and a raised LDH (295 u/l). B12 and folate levels were normal. Viral serology for hepatitis B, C, HIV and autoantibodies (ANA and anti dsDNA) were negative. G-6PD level was normal. Bone marrow biopsy was normal apart from erythroid hyperplasia. A chest x-ray, abdominal ultrasound (US) and CT scan did not reveal any abnormality apart from an enlarged spleen. He was continued on prednisolone 10 mg daily because of the evidence of ongoing haemolysis, along with folic acid and danazol. His Hb level remained stable over the next few days and he was discharged on above mentioned drugs with a follow-up plan. However, he was lost to follow-

up but continued his treatment at a local hospital.

One year after the diagnosis of AIHA, he was seen locally with a complaint of abdominal pain and weight loss and an US revealed multiple lymph nodes in the abdomen so he was again referred to our hospital with a possible diagnosis of lymphoma. He was still taking steroids. He had a low Hb (83g/l) with elevated markers of haemolysis and peripheral blood smear showed polychromasia, spherocytes and nucleated RBC (Figure 1). A CT scan of the abdomen confirmed the presence of multiple lymph nodes in the abdomen and pelvis along with hepatosplenomegaly (Figure 2). A biopsy from the para-aortic lymph node was carried out and confirmed the diagnosis of HD, mixed cellularity type (Stage III-B). He was started on ABVD chemotherapy which he tolerated well. Hb improved quickly so the prednisolone was tapered and stopped after the fourth cycle of chemotherapy. As there was persistent residual LAP and a borderline positivity on PET scan in some of the abdominal lymph nodes after 6 cycles of chemotherapy, he went on to complete 8 cycles. He has remained well with a normal Hb after one year of follow-up post chemotherapy.

### Discussion

AIHA is a recognized complication of lymphoproliferative disorders, especially chronic lymphocytic leukemia. HD, however, is rarely associated with AIHA. This association was first described by Eisner et al in 1967.<sup>2</sup> The reported frequency of Coombs' positive haemolytic anaemia in adults with HD has ranged from 0.2 percent in a large series of 492 patients from Europe<sup>3</sup> to 3 and 4 percent in two American studies.<sup>2,4</sup> These figures show that AIHA in HD is an uncommon association. When HD is accompanied by AIHA, the haemolysis is usually detected at the time of diagnosis or a relapse.<sup>4</sup> Very rarely has it been reported to precede the diagnosis of HD, in one case by up to 7 years.<sup>5,6</sup>

Both of our patients were diagnosed to have idiopathic AIHA one year before the diagnosis of HD. In majority of these patients, AIHA is associated with clinical or pathological evidence of stage III or IV disease.<sup>4</sup>

The exact mechanism of AIHA in HD is still not clear. However it may be postulated that the autoantibodies are directly produced by tumour cells or are related to an immune regulatory phenomenon. It is possible that there is an autoimmune process at the early stages of HD in which antibodies are produced against the tumour as well as the red blood cells as a para-neoplastic phenomenon. The antibodies prevent the growth of the tumour at least initially, which later escapes the anti tumour effect of the antibodies and finally manifests as HD. Although the specificity was not determined in our patient, the antibody associated with AIHA in some patients with HD has been identified as an

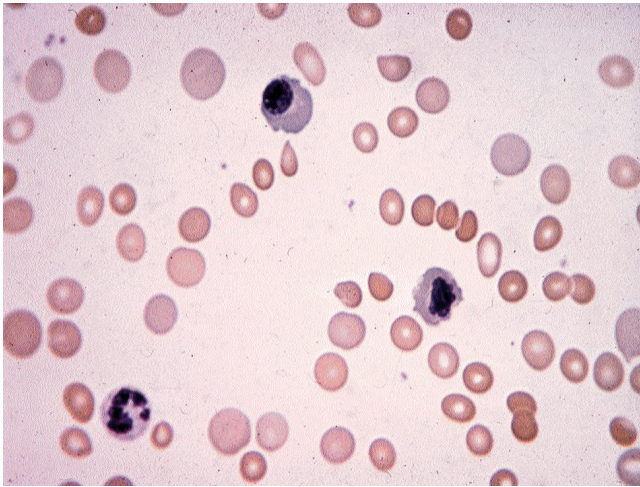


Figure 1: Peripheral blood smear of patient 2 at second visit showing spherocytes, polychromasia and nucleated RBC (H & E × 400).

anti transition (It) antibody.<sup>7</sup>

Patients with HD are known to have an impaired cell mediated immune response due to decrease in number as well as function of T lymphocytes. Decreased number of cytotoxic T cells could lead to excessive autoantibody production. This appears to be partly due to hyperactivation of B-cells. This concept is further strengthened by reports of high incidence of AIHA following T-cell depleted allogeneic bone marrow (BM) or peripheral blood stem cell (PBST) transplantation.<sup>8</sup> Treatment with anti CD20 antibody rituximab, which suppresses the B-lymphocytes, has shown to be effective in idiopathic AIHA as well as for immune haemolysis associated with BM or PBST transplantation.<sup>9,10</sup>

Acquired AIHA has been described to be associated



Figure 2: Abdominal CT scan of patient 2 before chemotherapy showing enlarged lymph nodes (arrows).

with an underlying disease in more than fifty percent of cases. Many patients with apparent idiopathic AIHA eventually manifest the presence of an associated disease.<sup>12</sup> HD is one of the conditions to be considered in the presence of warm agglutinin haemolytic anaemia. Although the initial treatment of AIHA is steroids, immune haemolysis associated with HD requires definitive treatment with systemic chemotherapy. Our patients presented with severe AIHA for which no etiology was found at initial presentation. Administration of steroids probably altered the course of the disease and made the diagnosis of HD difficult and late to establish. Some patients with AIHA may have a minimal tumour burden initially and the diagnosis of HD may be easily missed.<sup>13</sup> Our report illustrates that patients with AIHA should be regularly and carefully monitored, particularly in treatment resistant cases, for manifestations of a concomitant disease, such as HD, developing later.

## References

1. Jansch RH, Joosten, Achjanie SR, Arends JW, Volovics A, Hupperets PS, Schouten HC, et al. CD 44v6 is not a prognostic factor in primary breast cancer. *Ann Oncol* 1998; 9:109-13.
2. Eisner E, Ley AB, Mayer K. Coomb's positive hemolytic anemia in Hodgkin's disease. *Ann Int Med* 1967; 66:258-73.
3. Xiros N, Binder T, Anger B, Böhlke J, Heimpel H. Idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia in Hodgkin's disease. *Eur J Haematol* 1988; 40:437-41.
4. Levine AM, Thornton P, Forman SJ, Van Hale P, Holdorf D, Rouault CL, et al. Positive Coombs test in Hodgkin's disease: significance and implications. *Blood* 1980; 55:607-11.
5. Bowdler AJ, Glick IW. Autoimmune hemolytic anemia as the herald state of Hodgkin's disease. *Ann Intern Med* 1966; 65:761-7.
6. Cazenave JP, Gagnon JA, Girouard E, Bastarache A. Autoimmune hemolytic anemia terminating seven years later in Hodgkin's disease. *Can Med Assoc J* 1973; 109:748-9.
7. Garratty G, Petz LD, Wallerstein RO, Fundenberg HH. Autoimmune hemolytic anaemia in Hodgkin's disease associated with anti-It. *Transfusion* 1974; 14:226-31.
8. Horn B, Viele M, Mentzer W, Mogck N, DeSantes K, Cowan M. Autoimmune hemolytic anemia in patients with SCID after T cell-depleted BM and PBSC transplantation. *Bone Marrow Transplant* 1999; 24:1009-13.
9. Corti P, Bonanomi S, Vallinoto C, Balduzzi A, Uderzo C, Cazzaniga G, et al. Rituximab for immune hemolytic anemia following T- and B-Cell-depleted hematopoietic stem cell transplantation. *Acta Haematol* 2003; 109: 43-5.
10. Zecca M, Nobili B, Ramenghi U, Perrotta S, Amendola G, Rosito P, et al. Rituximab for the treatment of refractory autoimmune hemolytic anemia in children. *Blood*. 2003; 101: 3857-61.