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CASE REPORT

Congenital dyserythropoietic anaemia type II-like dysplastic anaemia preceding the development of non-Hodgkin lymphoma – a case report.

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Abstract

Anaemia is a frequent complication in patients with haematological malignancies and is caused by a variety of mechanisms including neoplastic cell infiltration into the bone marrow, haemolysis, nutritional deficiencies and defect in erythropoiesis or dysplastic anaemia as a result of the disease itself. However, acquired dysplastic anaemia which mimic congenital dyserythropoietic anaemia (CDA) type II morphology in the bone marrow is very rare. A 41-year-old Chinese man presented with refractory symptomatic anaemia in September 2001. He was clinically pale with no other significant physical finding. His initial peripheral blood picture showed normochromic normocytic anaemia with haemoglobin level of 26g/L, with no evidence of haemolysis and a poor reticulocyte response of 0.6%. Bone marrow aspiration was done and showed congenital dyserythropoietic anaemia (CDA) type II-like morphology. He was treated symptomatically with regular blood transfusions approximately every 3 weeks, until August 2002 when he developed multiple cervical lymphadenopathy with loss of appetite, loss of weight and low grade fever. Biopsy of the lymph node confirmed the diagnosis of small lymphocytic lymphoma. Staging with computed tomography and bone marrow aspirate revealed the infiltration of lymphoma cells into the marrow cavity consistent with the staging of IVB. This case report illustrates that CDA type II-like dysplastic anaemia can preceed the development of lymphoma.

Keywords: CDA type II-like morphology, non-Hodgkin's lymphoma.

INTRODUCTION

Anaemia is a frequent clinical complication of malignancy, more so in the haematological disorders. Various mechanisms had been documented to cause anaemia such as nutritional deficiency, haemolysis, bone marrow infiltration by neoplastic cells and dyserythropoiesis associated with the malignant disease itself.

Dyserythropoiesis is defined as defects in erythropoiesis and thus production of abnormal erythroid cells. It includes a wide variety of diseases in which some affect primarily the nucleus such as vitamin B12 and folate deficiency. Others affect predominantly the cytoplasm of which, the haemoglobin production may be impaired such as in iron deficiency anaemia. It is divided into two main categories i.e congenital dyserythropoietic anaemia (CDA) and secondary dyserythropoietic anaemia. CDA is a group of rare hereditary disorders characterized by refractory anaemia with abnormal multinuclearity of bone marrow erythroid precursors. Heimpel and Wendt[1] in 1968 classified CDA into three major types (Type I, II and III) based on the peripheral blood red cell morphology, bone marrow erythroblastic multinuclearity and positivity of the Ham's test.

Secondary dyserythropoietic anaemia is commonly associated with Human immunodeficiency virus (HIV) infection, chronic infection such as tuberculosis, drug-induced or neoplastic cell infiltration of bone marrow. These dysplastic changes of the erythroid cells are usually seen during or even following the active disease. There have been case reports disclosing the association of monoclonal gammopathy of undetermined significance, myeloma and

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malignant lymphomas with CDA type III.[2,3,4] There is scanty documentation of severe dysplastic anaemia preceding the development of lymphoma or of dysplastic changes that mimic the CDA type II like erythroid morphology.

We report here a 41-year-old man who developed a very rare CDA type II-like dysplastic anaemia, which preceded the development of non-Hodgkin lymphoma.

CASE REPORT

A 41-year-old Chinese man presented to Hospital UKM in September 2001 for worsening symptomatic anaemia for about a month prior to admission. No other symptoms like chest pain, orthopnoea, loss of appetite, loss of weight, fever or bleeding tendency was present. However, he claimed to have taken some herbal medicine that he bought over the counter for about 2 weeks and noted to have yellowish discoloration and pallor of the skin and subsequently had developed bilateral leg swelling. He did not smoke or consume alcohol. No other significant past medical or surgical history was elicited. Physical examination at that time showed that he was pale, jaundiced with bilateral ankle oedema. Vital signs were otherwise normal. Examination of the cardiovascular system and respiratory system were normal. No obvious organomegaly or lymphadenopathy was noted.

Investigation of the complete blood count showed haemoglobin, 29g/L; red blood cell count, $1.41x10^{12}$/l; packed cell volume, 9.3%; mean corpuscular volume, 65.6fl; mean corpuscular haemoglobin, 20.5pg; reticulocyte count, 0.6%; white blood cell count, $16.4x10^{9}$/l; platelet count, $174x10^{9}$/l. Serum lactate dehydrogenase (LDH) was very high, 1998 U/L; both direct and indirect coombs' test were negative; urine urobilinogen and haemosiderin were negative. Haemoglobin electrophoresis showed no abnormal band, Hb A_2 3.2% and Hb F 1.0% and H inclusion was negative. Ham's acidified serum haemolysis test was negative. Glucose-6-phosphate dehydrogenase (G6PD) screen was normal with G6PD assay 216miu/10^{9}. Osmotic fragility test showed that a portion of his red cells shifted to the left, indicative of their resistance to osmotic lysis. Erythrocyte sedimentation rate (ESR) was 38mm/hr. Investigations of the viral hepatitis serology (Hepatitis B, C), HIV, Ebstein Barr Virus (EBV) IgM & IgG and Toxoplasma IgG were all unremarkable. Mycoplasma IgM was <1/40 but IgG was negative. Connective tissue screening for anti-nuclear antibody (ANA) was negative. He was transfused with 6 units of packed red cells without any complication.

However, about 1 month after the initial presentation, he again presented with

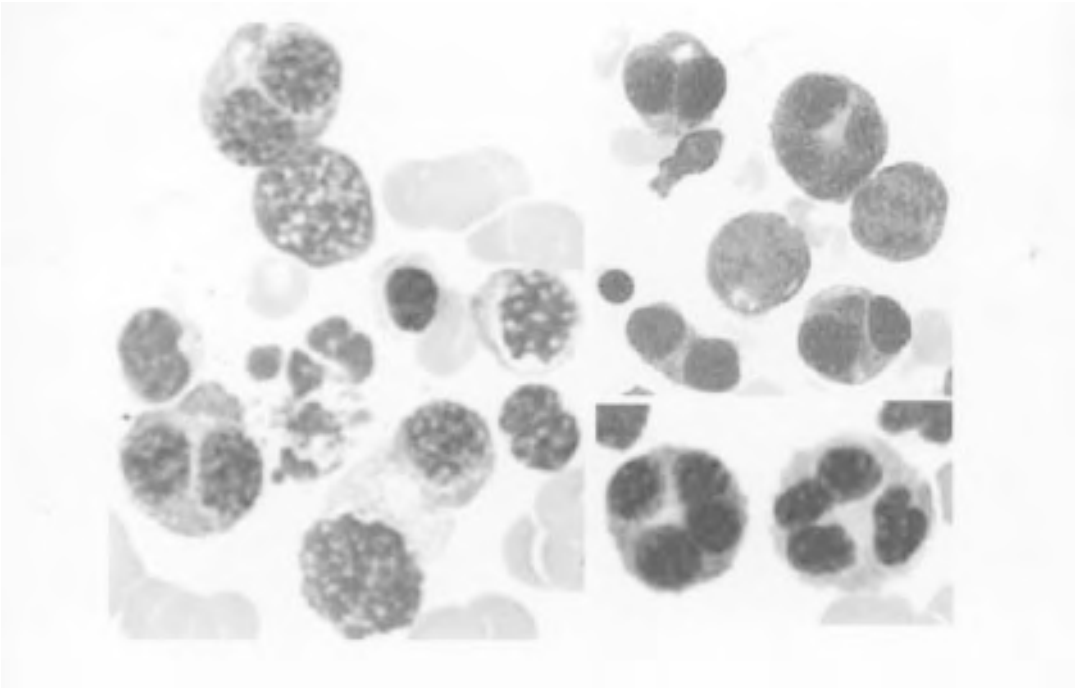

Fig. 1: Bone marrow aspirate showing multiple binucleated and multinucleated erythroblasts with mild megaloblastic changes mimicking CDA type II morphology. X 400.

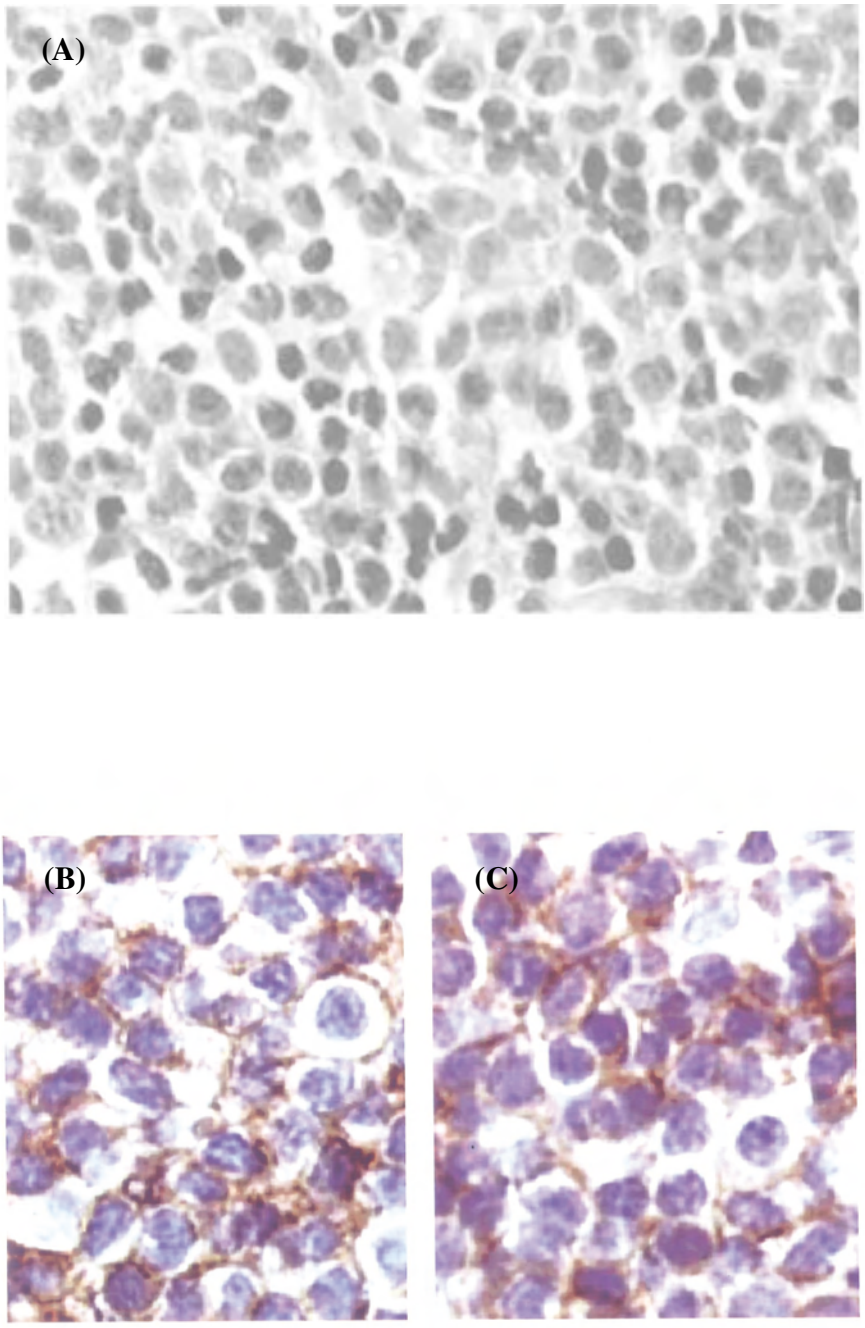

Fig. 2: Lymph node showing diffuse infiltration with small lymphoid cells (A) which stain positive for LCA (B) and CD20 (C) consistent with lymphoma of B cell type. X 400.

symptomatic anaemia with a haemoglobin level of 46 g/L. In view of the persistent anaemia, bone marrow aspiration was performed in December 2001. It showed erythroid hyperplasia and marked dyserythropoietic changes with presence of binuclearity and multinuclearity of the erythroid precursor cells (Fig. 1). Cytoplasmic bridging and megaloblastic changes were also observed. A provisional diagnosis of congenital dyserythropoietic anaemia (CDA)-type II was made based on the marrow findings. Since then, he required regular packed red cell

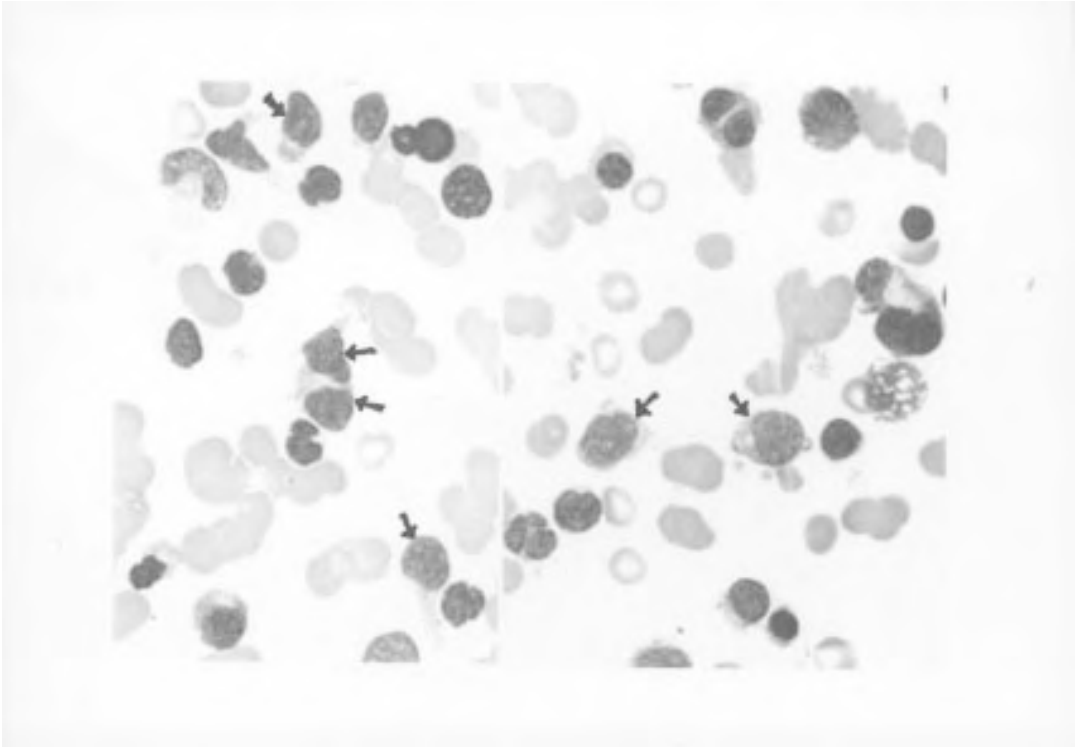

Fig. 3: Repeat bone marrow aspirate done for staging of lymphoma showing many abnormal lymphoid cells (arrow) in a background of dyserythropoietic anaemia changes (multinucleated erythroblasts). X 100.

transfusion every three weeks with the pretransfusion haemoglobin levels of about 30-40 g/L.

About 8 months after the diagnosis of CDA, he claimed to have developed multiple right neck swellings, associated with loss of appetite, loss of weight and low-grade fever. Histopathology of the right supraclavicular lymph node biopsy (Fig. 2) was consistent with a well-differentiated lymphocytic lymphoma. The tumour cells showed strong immuno-positivity for leukocyte common antigen (LCA), CD20 and CD79α. A repeat bone marrow aspiration (Fig. 3) showed that the erythropoiesis was quantitatively normal but with persistence of dyserythropoietic changes of binuclearity, trinuclearity, cytoplasmic bridging and ragged cytoplasm of erythroid precursors. Numerous smudge cells of undetermined origin and abnormal lymphoid cells (15%) were infiltrating the cell trails indicative of bone marrow infiltration by abnormal lymphoid cells (Fig. 3). Immunophenotyping of the bone marrow mononuclear cells showed that these cells expressed CD5, CD19, CD20, CD23, CD11c, HLA-DR, surface IgG and IgD consistent with lymphoma infiltration of the bone marrow.

The patient was then planned for 6 courses of CHOP (cyclophosphamide, doxorubicin, vincristine & prednisolone) to be followed by stem cell transplantation. Unfortunately, after the first course of CHOP, he succumbed to bronchopneumonia and septicaemia.

DISCUSSION

Dyserythropoietic anaemia depicts any alteration of the normal differentiation-proliferation pathway of the erythroid lineage. It appears to be both a qualitative and quantitative defect of erythropoiesis and occurs in a wide range of diseases embracing a number of conditions which primarily affect the nucleus or the cytoplasm of the erythroblasts in an environment at which erythropoiesis takes place. Dyserythropoietic anaemia can be primary i.e congenital dyserythropoietic anaemia (CDA) or secondary to some diseases such as nutritional anaemia, myelodysplastic syndrome, liver disease, HIV and malaria infections, post bone-marrow transplantation and following chemotherapy.

Congenital dyserythropoietic anaemia comprises a group of hereditary disorders of erythropoiesis characterized by ineffective

erythropoiesis as the predominant mechanism of anaemia and distinct morphological abnormalities of the bone marrow erythroblasts, and is classified into three classical types (type I, II and III). Most cases of CDA are diagnosed early in life. Our patient was diagnosed at the age of 41 years with clinical presentation and bone marrow morphology compatible with CDA type II except for the negative Ham's test, the severity of the anaemia, and the clonal evolution of non-Hodgkin's lymphoma within a short interval. These findings raise the question whether this is an acquired dyserythropoietic anaemia.

Achille *et al*[5] in 2001 had shown that a small percentage of these cases had late diagnosis, with the age at diagnosis ranging from 4 months to 65 years (mean, 15.9 ± 11.8 years). Other authors too have reported cases of CDA diagnosed at the age of 43 years [4] and 71 years[6] respectively. Wickramasinghe[7] in 1998 identified that one third of dyserythropoietic anaemias do not fulfill the initial diagnostic criteria and are types other than the classical types. Bianchi *et al*[3] in 1998 also reported two cases of CDA type II which were Ham's test negative and were named as CDA type II variant. Besides, literature review showed a few adult onset CDA cases, especially CDA type III, to be associated with the development of haematological malignancies after many years.[2,3,4] A patient, who was diagnosed as CDA type III at the age of 43 years, developed malignant T-cell lymphoma about 17 years later.[4] Sandstrom *et al*[2] in 1994 also studied a family of CDA type III and noted a high prevalence of monoclonal gammopathy of undetermined significance in 3 out of 20 patients and myeloma in 1 of 20 patients. Therefore, there may be an increased risk of development of haematological malignancies in patients with CDA.

Or patient, who presented with very severe anaemia, bone marrow morphology that mimicked CDA type II, had a negative Ham's test and develop lymphoma about a year later. This is more suggestive of an acquired dysplastic anaemia which may be a prodrome of lymphoma evolution. It is interesting to highlight the morphology of dysplastic anaemia that mimics the CDA type II in this case report.

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