The differential diagnosis of HIV related anaemia should include pure red cell aplasia

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Abstract

Hematologic abnormalities feature commonly in patients with human immunodeficiency virus (HIV) infection. This includes anaemia and it occurs in 70 – 80% of patients. The causes of HIV-related anaemia are multifactorial. The possible mechanisms causing the anaemia are those which are directly related to HIV and include infection, malignancy, drugs, anaemia of chronic disease, haemolysis, blood loss and hypersplenism, whilst there are multiple causes not related to HIV. Features found in HIV-related anaemia can be ascribed to a disturbance of the bone marrow cytokine homeostasis. HIV is cytotoxic to T-helper lymphocytes which in turn retards growth of bone marrow progenitors. The most common abnormal finding is dysplasia affecting one or more cell lines. A predominant finding is erythroid dysplasia which is seen in over 50% of HIV patients. Hematologic complications related to combined antiretroviral therapy (cART) add to the diagnostic challenge. Pure red cell aplasia (PRCA) is an uncommon hematologic disorder that causes anaemia. However in patients that present with normochromic normocytic anaemia, in particular those that are transfusion dependent, pure red cell anaemia should be considered. In patients with AIDS, the mechanisms postulated for PCRA is the autoimmune response as a consequence of immune-dysregulated status in AIDS and the second being the myelosuppressive effect of antiretroviral therapy.

Case report

A 30-year old female presented to the Steve Biko Academic Hospital in December 2011 complaining of lethargy, palpitations, dizziness and exertional dyspnoea for a week. Her background history was that she was diagnosed with human immunodeficiency virus (HIV) in 2006 but not on combined antiretroviral therapy (cART) and endometriosis is 2008. Both her parents were also diagnosed with HIV. On clinical examination, her blood pressure was 102/62 mmHg, pallor was confirmed with lymphadenopathy (submandibular and cervical measuring 1 – 2 cm in diameter) and an ejection systolic murmur. On admission her haemoglobin was 7.4 g/dL with a normal MCV and MCHC, a normal serum ferritin and increased serum vitamin B12 (837 pmol/l) and serum folate. Her absolute CD4 count was 262 x 10^6/l. Hepatitis A, B and C antibodies were all negative. A lymph node biopsy was done to exclude malignancy and the result was suggestive of non-specific reactive changes with no evidence of a specific infection or neoplasia. Bone marrow biopsy was performed to exclude haematological malignancy. The bone marrow specimen was reported to be suboptimal and not a true representation of marrow. A final haematological diagnosis could not be made and a repeat marrow investigation was suggested by the pathologist should the anaemia not improve. The patient was discharged on Tenofovir, Efavirenz and Lamivudine.

She presented 10 months later with the same symptoms having had multiple blood transfusions since her discharge. During this readmission, she had pallor, blood pressure of 106/86 mmHg with good air entry bilaterally on lung auscultation, no lymphadenopathy but hepatomegaly of 14cm. However, her haemoglobin had dropped to 5.1 g/dL. Her CD4 had increased to 449 x 10^6/l. Tests performed at this time included a liver biopsy which showed severe hemosiderosis, PCR for human Parvovirus (HPV) B19 was negative, an ultrasound scan was done to exclude thymoma and a new bone marrow aspirate and biopsy was performed. The bone marrow morphological picture was consistent with that of pure red cell aplasia (PRCA). The bone marrow was normocellular with reduced erythropoiesis with a maturation block at the level of pronormoblast.

Discussion

PRCA is a rare haematological disorder which is characterized by severe anaemia, reticulocytopenia and almost complete absence of erythroid precursors in the bone marrow.[1] The pathophysiology of PRCA is heterogeneous and may be congenital or acquired.[1] The study by Charles et al examined 37 patients with PRCA prospectively. 51% of these patients had other conditions known to be associated with PRCA. Immunologic disorders like rheumatoid arthritis were present in 14%. A history of previous autoimmune disease eg, Hashimoto's thyroiditis was reported in 11%. Infections like HIV or Epstein Barr virus was present in 5% with lymphoma or chronic lymphocytic leukaemia in 8%. A history of previous or recurrent thymoma was reported in 8%. [2] The analysis of the study by Charles et al, indicated that PRCA involves three mechanisms: immunologically mediated disease including T-cell or antibody mediated inhibition of erythropoiesis, HPV B19 infections (which specifically infects and lyses erythroid progenitor cells) and an intrinsic stem or multipotent progenitor cell defect i.e. myelodysplsia.[2] In patients with AIDS, however, the mechanisms postulated for PCRA is the autoimmune response as a consequence of immune-dysregulated status in AIDS and the second being the myelosuppressive effect of antiretroviral therapy.[3]

The literature does describe zidovudine (ZDV) and lamuvidine (3TC) induced pure red cell anemia.[3,4] PRCA has been documented to occur from six weeks of therapy to within three months of 3TC and ZDV therapy.[3] Patients with HIV-1 infection commonly develop pancytopenia, with the causes being iatrogenic or multifactorial. The most consistent haematopoietic defects that occur in seropositive patients as a result of HIV-1 infection per se include, firstly, regenerative bone marrow failure in which on-demand haematopoiesis is suppressed and secondly, a high frequency of unusually aggressive extranodal non-Hodgkin's lymphomas.[5] It should be highlighted that bone marrow abnormalities are frequently observed in HIV infected individuals at all stages of the disease.[6] Thus examination of the bone marrow in HIV infected individuals is usually performed to evaluate peripheral cytopenias or when systemic infections or malignancies are suspected.[66.]

Haematological complications especially anaemia in HIV is common. The aetiology of which is usually multifactorial. The diagnosis of PRCA is based on marrow findings and this case highlights the need for bone marrow aspirate and biopsy in patients with HIV who present with severe anaemia. Research has shown that PRCA is amenable to therapy and that remissions can be obtained in most patients.[2] Specific treatment suggested is initial therapy with prednisone. A second line agent like cyclosporine or cyclophosphamide can be used if corticosteroids do not produce a remission within six weeks, provided there are no

contraindications. Patients with concomitant medical conditions like large granular lymphocytic leukaemia may benefit with low dose methotrexate. In vitro erythroid culture has also been suggested as an alternative therapy for those patients refractory to prednisone and a second-line agent.[2]

References

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