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Case Report

Acute B Cell Lymphoblastic Leukaemia and Human Immunodeficiency Virus Infection (HIV)

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Highly active anti-retroviral therapy (HAART) and prophylactic therapy for opportunistic infection have significantly improved the survival and quality of life for patients infected with the Human Immunodeficiency Virus (HIV).[1,2]

Lymphoproliferative disease complicates the clinical course of HIV infection in approximately 10% of patients and the incidence of Non Hodgkins Lymphoma is 60-200 times more common than the general population.[3,4] Diffuse large B cell lymphoma, Burkitt's Lymphoma, Burkitt like Lymphoma and Primary Cerebral Lymphoma are the most common subtypes with Hodgkins Disease, Plasmacytoma and Body Cavity Based Lymphomas also increased in incidence.[4] Acute B cell lymphoblastic leukaemia (B ALL) is uncommon representing 5% of all adult patients with ALL.[5] An association with HIV infection is rare and limited to case reports. We report the case of a 40 year old man and discuss his treatment and clinical course. We suggest that B cell ALL should be included in the criteria for a diagnosis of the Acquired Immunodeficiency Syndrome (AIDS) and that patients presenting with this type of leukaemia should be fully assessed regarding risk factors for HIV infection and when necessary tested following appropriate counselling. We support present recommendations that patients with HIV associated lymphoproliferative disease receiving chemotherapy should receive concurrent HAART and when possible are entered into clinical trials where the maximal therapy can be addressed.

CASE REPORT A 40 year old homosexual male presented to a District General Hospital in March 1999 with a short history of a chest infection, shortness of breath, night sweats, weight loss and left facial weakness. Physical examination revealed a complete left lower motor neurone facial nerve palsy, dullness and crepitations at the right base and smooth hepatosplenomegaly. There was no peripheral lymphadenopathy sternal tenderness or testicular enlargement. He had been previously well and working as a fitness instructor. Six years previously he attended a genitourinary clinic where he tested positive for HIV. He declined treatment at this time and was lost to review.

INVESTIGATIONS

Haemoglobin was 10 g/dl with a platelet count of 135 x 10^9/l and a white cell count of 9.6 x 10^9/l. The differential white cell count revealed lymphocytes at 4.0 x 10^9/l, neutrophils at 4.5 x 10^9/l, monocytes at 0.8 x 10^9/l and blasts cells of L3 morphology at 0.2 x 10^9/l. Lactate dehydrogenase (LDH) was 10 828 iu/l with a urate level of 0.58 mmol/l.

Chest radiograph showed a right hilar mass with an associated pleural effusion. Subsequent pleural aspiration revealed the presence of blast cells.

Computerized axial scanning (C.T.) confirmed the chest findings and hepatosplenomegaly. C.T. scan of the brain was normal however Cerebrospinal fluid (CSF) examination revealed L3 blast cells. Bone marrow aspirate and trephine

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biopsy revealed a packed marrow with blast cells exhibiting characteristic L3 morphology with basophilic cytoplasm and vacuolation. (Figure). Immunophenotype of these blast cells revealed strong positivity for the B cell markers CD19 and CD22 with weaker expression of CD10. Terminal deoxynucleotidyl transferase (TDT) was negative. This immunophenptype in combination with the morphological findings was in keeping with a diagnosis of Acute B cell Lymphoblastic Leukaemia. Virology confirmed HIV positivity with a viral load of 1.3 x 10^6 copies per/ml.

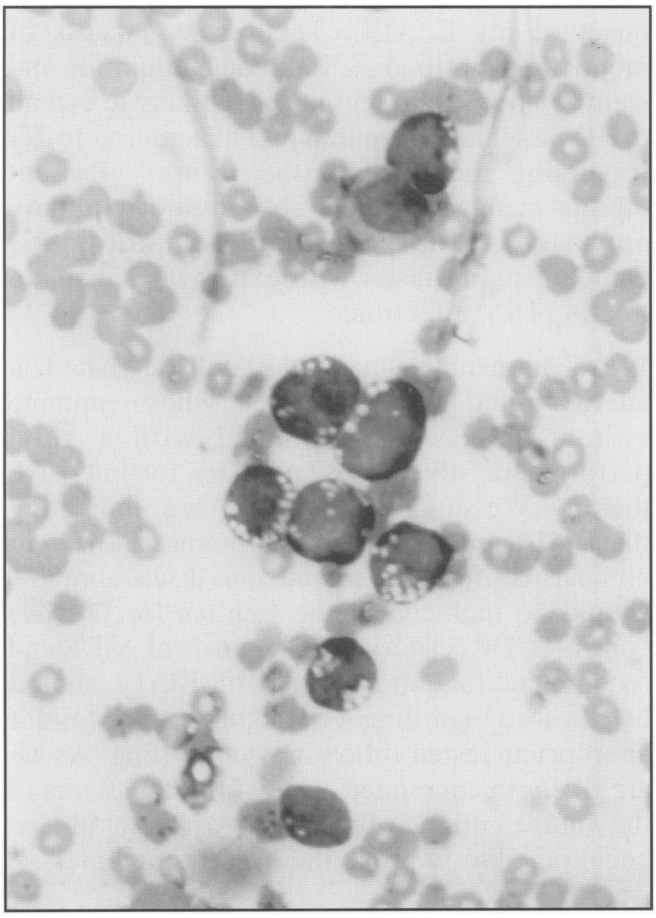

Fig. Bone marrow aspirate showing blast cells of L3 morphology exhibiting basophilic and vacuolated cytoplasm. (Wrights Stain)

Hepatitis A B C, Epstein Barr Virus and Cytomegalovirus all tested negative and the CD4+ve lymphocyte count was 475 µ/l. Due to biohazard regulations within the Cytogenetics Laboratory we were unable to obtain a cytogenetic result.

TREATMENT

He received combination chemotherapy with the COP/COPADM/mini CYVE regimen. This containing combinations of the drugs cyclophosphamide, vincristine, prednisolone, doxorubicin, ARA-C, etoposide and methotrexate. High dose methotrexate was administered at a dose of 8 gm/m.[2] Intrathecal chemotherapy was given and followed by cranial irradiation.

He declined anti-retroviral therapy initially however following discussion this was commenced in August 1999 with zidovudine, lamivudine and efavirenz. Repeat viral load was <150 copies/ml in December 1999. Chemotherapy was well tolerated with no opportunistic infections and interestingly a period of prolonged thrombocytopenia responded to commencement of the anti-retroviral therapy. Co-trimoxazole and fluconazole prophylaxis were administered.

Haematological remission was achieved in his blood and bone marrow with resolution of the chest x ray appearances. Despite the absence of blasts in his CSF there was no resolution of his facial nerve palsy. He had 2 HLA matched siblings and was considered for allogeneic transplantation however his remission was short lived and he relapsed 2 months later within his chest, CSF and bone marrow with an LDH measuring 40 000 µ/l. Despite further attempts at re-induction he was unable to achieve a complete second remission and died in February 2000.

DISCUSSION

Highly active anti-retroviral therapy (HAART) and prophylactic therapy against opportunistic infection have significantly decreased the morbidity and mortality associated with the Human Immunodeficiency Virus (HIV).[1,2] Lymphoproliferative disease complicates the clinical course in approximately 10% of patients. This incidence may be decreasing since the introduction of HAART as suggested in a recent meta-analysis and appears most marked for Primary Cerebral Lymphoma.[3] The pathogenesis is not completely understood however continued B cell proliferation in the absence of normal T cell immunosurveillance is a likely factor with the Epstein Barr Virus implicated in many cases.[3,4] Rarely HIV may be directly oncogenic in T cell lymphomas and Human Herpes Simplex Virus 8 (HHV 8) has been implicated in Body Cavity Based Lymphoma.[4] Treatment is difficult as the disease is often advanced at diagnosis with extranodal and bone marrow involvement present. The risk of opportunistic infection is increased with

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intensive chemotherapy and viral induced myelodysplasia may delay recovery of bone marrow function.[3] There is also a concern that chemotherapy may exacerbate HIV infection. Adverse prognostic features are a poor performance status, a prior diagnosis of AIDS (Acquired Immune Deficiency Syndrome), CD 4 lymphocyte count <100 μ/l and extranodal disease, particularly central nervous system involvement. The overall survival is usually less than 1 year.[6] Several chemotherapy regimens have been investigated and an initial randomised trial comparing a low dose and standard dose chemotherapy regime (mBACOD) with granulocyte – macrophage colony stimulating factor (GIVI-CSF) support showed no difference in response or survival in the two groups however there was an increase in the incidence of neutropenic sepsis in the full dose arm.[7] Recently developed protocols have resulted in improved response and survival rates, particularly in good risk patients. There is also the suggestion of improved survival since the introduction of HAART in 1996 with further studies required for confirmation.[8, 9]

Acute B cell lymphoblastic leukaemia (B ALL) is characteristically associated with central nervous system involvement and a poor prognosis. The cytogenetic abnormality t(8:14) is present in the majority of cases this resulting in dysregulation of the c-myc proto-oncogene which is implicated in pathogenesis. Morphology is characteristic with blast cells exhibiting strongly basophilic cytoplasm and vacuolation (Figure). Recent intensive protocols incorporating high dose methotrexate and ARA-C have shown improved survival rates in both children and adults.[10]

B ALL in association with HIV is rare and limited to case reports. Approximately 22 cases have been reported to date.[11] In most previously reported cases there was no history of AIDS and the CD 4 count was reasonably well preserved at diagnosis.[11] This pattern of presentation was similar in our patient. Treatment with intensive combination chemotherapy was well tolerated and no atypical opportunistic infections were encountered. An episode of prolonged thrombocytopenia of less than 20 x 10^9/l for 5 months responded to the initiation of anti-retroviral therapy with counts improving to 70 x 10^9/l and was suggestive of viral induced thrombocytopenia. Prior to relapse this patient had been considered for an allogeneic bone marrow transplant, syngeneic transplantation having previously been described in an HIV positive haemophiliac patient with ALL.[12] The poor survival of our patient was similar to the majority of cases reported.

The impact of HAART on survival remains to be seen and although overlapping toxicities and interactions may occur it is recommended all patients receive this therapy in combination with chemotherapy. Although more evidence is awaited it is possible that had our patient received anti-retroviral therapy earlier in the course of his infection this may have delayed or prevented the onset of his B ALL. The recent success of monoclonal antibodies, immune modulation and stem cell transplant regimens are likely to extend to HIV associated lymphoma/leukaemia and offer promising therapies in the future.[13] Present optimal management requires a multidisciplinary approach with specialist Haematologists/ Oncologists in liason with expert physicians in treating HIV infection.

We recommend that patients should be treated on an individual basis and those whose immune system is less compromised with a good performance status are candidates for intensive therapy. We suggest that a statement indicating that B ALL and Burkitt's Lymphoma are different clinical manifestations of the same disease process should be included in the Centres for Disease control (CDC) criteria for diagnosis of AIDS and recommend that all patients with B ALL should be assessed regarding risk factors for HIV and if appropriate tested following counselling. As we are likely to encounter more of these patients in the future entrance to clinical trials should be encouraged to improve the overall outcome.

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