Acquired Immunodeficiency Syndrome Presenting as Childhood Non-Hodgkin's Lymphoma

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ABSTRACT

Two children with non-Hodgkin's lymphoma (NHL) as the presenting illness of acquired immunodeficiency syndrome (AIDS) are described. There was a delay in diagnosing the underlying AIDS in both cases. In the first case, an 18-month-old boy with stage IV, high-grade, T-cell NHL, the diagnosis of underlying AIDS was suspected only when he developed recurrent and profound opportunistic infection during chemotherapy. The second case, an eight-month-old female infant presented initially with hepatosplenomegaly and thrombocytopenia of undetermined cause. She had progressive abdominal distension and swelling of her right eye one year later due to high grade B-cell NHL. She was later found to be sero-positive for HIV during pre-chemotherapy screening. As the prevalence of HIV infection continues to increase, HIV infection should be considered in the differential diagnoses of childhood hepatosplenomegaly and thrombocytopenia, and as a possible underlying cause of childhood cancer, especially NHL.

Keywords: non-Hodgkin's lymphoma, AIDS, childhood

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INTRODUCTION

The human immunodeficiency virus (HIV) epidemic continues to spread and affect communities around the world. According to estimates by the Joint United Nations Program on HIV/Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS) and the World Health Organization (WHO), nearly 31 million people were living with HIV/AIDS by the end of 1997[1]. Of these, 1.1 million were children under 15 years of age. In Malaysia, as of 31 December 1997, the Malaysian Ministry of Health has reported a total of 24,002 people infected with HIV, with approximately 300 new HIV infections and 40 AIDS cases recorded per month[2]. However, the actual prevalence of HIV infection could be much higher[3].

Common malignancies seen in childhood HIV infection include Burkitt's lymphoma, non-Hodgkin's lymphoma (NHL), primary central nervous system lymphomas, and leiomyosarcomas[4,5]. HIV infection should be considered in any children presenting with these malignancies[6]. We describe two cases of childhood HIV infection who presented with NHL. In both instances, underlying HIV infection was missed initially.

CASE REPORT

Case 1

An 18-month-old boy was referred for fever and abdominal distension of two weeks' duration. He was delivered after a full term and uneventful pregnancy to a Thai mother, and was given for adoption soon after birth. Prior to admission, he enjoyed good health and had never been transfused. Examination on admission showed a pale child with gross hepatosplenomegaly and generalised lymphadenopathy, involving cervical, axillary and inguinal regions. The haemoglobin level on admission was 109 g/L and white cell count was 4.0 x 10^9/L. Coomb's test was positive. CT scan of chest and abdomen showed mediastinal and para-aortic lymphadenopathy. Lymph node biopsy, bone marrow aspiration and trephine biopsy examination showed diffuse high-grade immunoblastic NHL (T cell type), with bone marrow involvement. He was commenced on induction therapy with prednisolone, vincristine, daunorubicin and intrathecal methotrexate (BFM - ALL 1989 protocol). His disease responded well to chemotherapy. He was in clinical remission but developed systemic candidiasis after two courses of vincristine and daunorubicin.

The patient subsequently defaulted further treatment. He returned three months later with fever, spontaneous bruises, and cervical lymphadenopathy. Similar induction chemotherapy was recommenced. However, the chemotherapy was complicated by more opportunistic infections than one would usually expect: Pneumocystic carinii pneumonia, pulmonary aspergillosis, and systemic candidiasis. Other underlying immunodeficiency states, apart from lymphoma and

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its treatment, was suspected. Determination of lymphocytes subset showed a markedly reduced CD4+ T lymphocytes (CD4+ 237 cells/μL, CD8+ 1971 cells/μL) and a CD4+ / CD8+ ratio of 0.12. Serological test with EIA method for HIV infection was positive. This was later confirmed with the Western Blot method. Further chemotherapy was abandoned at the request of the adoptive parents. The child was started on oral cotrimoxazole and itraconazole prophylaxis and three-weekly intravenous immunoglobulin infusion. He remained relatively well for the next two-and-half years and was free of major infections.

Three-and-half years after the initial presentation of NHL, the patient complained of bilateral leg weakness. A cranial CT scan showed bilateral basal ganglia calcification and diffuse cerebral atrophy, reflecting central nervous system involvement in AIDS[7]. Over the following one year, he had regression of developmental milestones. He succumbed to a febrile illness four years and ten months after the initial presentation. There was no clinical evidence of relapse of NHL. No autopsy was performed.

Case 2

An eight-month-old female Chinese infant first presented to a local hospital with fever and diarrhoea. The patient was the only child of a very young couple. She was born at full term, with a birth weight of 3.0 kg. The pregnancy was uneventful. The father, who is 27 years old, works as a carpenter while the mother, 19 years old, is a housewife. There was no forthcoming history of HIV/AIDS from the parents. Physical examination at that time showed that the liver was 4 cm and the spleen was 6 cm palpable below the right and left costal margins respectively. The haemoglobin was 86 g/L, white cell count was 9.1 x 10^9/L (neutrophils 54%, lymphocytes 46%) and platelet count was 23 x 10^9/L. She was referred to this hospital for further investigations. A peripheral blood film examination showed a few atypical lymphocytes and a reduced number of platelets. She improved a few days after admission, with a reduction in the sizes of liver and spleen. The platelet count increased to 131 x 10^9/L. She was then discharged with a diagnosis of viral fever.

On review at the age of eleven months she was found to be thriving well, growing along the 10th percentile for both weight and length. The liver was 4 cm and the spleen was 3 cm palpable below the right and left costal margins, respectively. The platelet count was 16 x 10^9/L, haemoglobin was 85 g/L, and white cell count was 11.5 x 10^9/L (neutrophils 8%, lymphocytes 73%, eosinophils 2%, atypical lymphocytes 10%). Bone marrow aspiration and trephine biopsy examinations were reported as normal. Screening for TORCH infections was negative. Subsequent follow-up showed persistent anaemia and thrombocytopenia, an enlarged liver and spleen, and cervical and axillary lymphadenopathy. A repeat bone marrow examination was advised but was refused. The child was subsequently lost to follow-up. She was never transfused during her admission.

At the age of two years, the patient was admitted again to this hospital with progressive swelling of the abdomen and the right eye of one-month duration. Examination showed a pale child with both weight and length on the third centiles. There was a swelling of the right eyelid, and the abdomen was distended. The liver was enlarged at 5 cm and the spleen at 5 cm below the costal margins. A firm, irregular non-ballotable mass, 7 cm in diameter was palpable at the left iliac fossa. There was generalised lymphadenopathy. The clinical diagnosis was NHL.

The following investigations were performed: haemoglobin 122 g/L, white cell count 15.7 x 10^9/L, and platelet count 256 x 10^9/L. Cranial CT scan showed a soft tissue mass in the periorbital region of the right eye, and an extradural mass posterior to the right orbit in the temporal fossa. Ultrasound examination of the abdomen revealed multiple liver nodules and a large soft tissue mass in the left side of the abdomen. A bone marrow aspiration and trephine biopsy examination showed no evidence of malignancy, and a fine needle aspiration cytology of the left iliac fossa mass confirmed NHL, high grade B-cell type. Pre-chemotherapy screening for HIV serology with ELISA was positive on two occasions. This was confirmed by Western blot. The CD4 count was 1,363 cells/μL (15%) and CD8 4,544 cells/μL (50%). She was started on oral cotrimoxazole and nystatin prophylaxis, and dual anti-retroviral therapy (zidovudine and DDI). She completed her anticancer chemotherapy (BFM B-NHL 1987 protocol for stage lV disease) in three-and-a-half months and went into clinical remission. The repeat lymphocyte subset four months after HIV chemotherapy showed CD4 count 221 cells/μL (32%), CD8 393 cells/μL. Over the next few weeks, she developed *Pneumocystis carinii* pneumonia, became profoundly hypoxic, and required mechanical ventilation. She finally succumbed six months after the initial diagnosis of AIDS and NHL.

The parents were both screened for HIV infection after counselling, and were found to be HIV seropositive. The father acknowledged that he had visited commercial sex workers in a neighboring country before marriage. Both parents are under treatment presently.

DISCUSSION

We presented two young children with high grade, NHL who were later found to have underlying HIV

infection. NHL was the AIDS-defining disease in both instances and both children acquired the infection vertically. In the first case, the underlying HIV infection was suspected only when the child developed numerous and profound opportunistic infections, which were more severe than one would normally expect to find when treating NHL without underlying AIDS. Because of the experience of the first case, serological screening for HIV infection was performed before commencing chemotherapy in children with malignancy in this hospital. Thus, in the second case, the underlying HIV infection was diagnosed when HIV serology screening before commencing anticancer chemotherapy was positive. There was no other clinical or laboratory evidence to suggest involvement of other systems by AIDS at the time of diagnosis of NHL. However the initial clinical picture at eight months of age with enlarged liver and spleen and thrombocytopenia could have been caused by HIV infection. About 5 - 10% of HIV seropositive individuals, in all risk groups, develop a syndrome of immunological thrombocytopenic purpura[8]. The precise mechanism of this thrombocytopenia remains unclear. The lack of suspicion of HIV infection, absence of history of high-risk behaviour in the parents and the loss of subsequent follow-up caused a delay in the diagnosis of underlying HIV infection in this second case.

In 1994, 1.7% of the 6,209 children with AIDS registered with Centers of Disease Control and Prevention were noted to have cancer as their AIDS-indicator disease[9]. Lymphoma was found to be the initial AIDS-defining condition in 43% of childhood HIV infection with malignancy in one series from the United States[5]. The majority of the NHLs were high-grade B-cell tumours, as seen in the second case[5]. The relative risk for a child with HIV infection to develop NHL was calculated to be 1,200 to 2,500 times greater than expected in healthy children of the same age[5,6]. Hence, it has been suggested that HIV infection may need to be considered as a predisposing cause of childhood cancer, especially in NHLs[6]. This case report reinforced the importance of screening for HIV infection in any childhood malignancy, especially in NHL. A recent study conducted in Kinta Valley, Malaysia, using unlinked anonymous testing of newborns, showed that the seroprevalence of HIV infection was 27 times higher than the number of reported cases within the same region[10]. Hence, it is envisaged that paediatricians caring for children with cancer would encounter more AIDS-related malignancies in the future.

The prognosis for NHL in AIDS is poor[5,6]. The median survival after NHL diagnosis was six months in the series reported by Granovsky et al[5], while in the series reported by Evans et al, six of the seven children with NHL died at a median of 6.5 months after the initial diagnosis of AIDS[6]. This poor prognosis is thought to reflect the rapidly progressive HIV disease, as observed in 20 - 25% of vertically transmitted AIDS[11]. Other poor prognostic factors were younger age at presentation and a low CD4 percentage at presentation[5]. However, both the cases reported here achieved remission after anticancer chemotherapy. In the first case, the child survived for nearly five years after the initial diagnosis of NHL even though the chemotherapy was not completed. The second child died of AIDS while in complete remission after the completion of the cytotoxic chemotherapy.

The decision to treat a malignancy in a child with HIV infection must be guided by the stage of the cancer and the general status of the child. If treatment is initiated, the intention should be to cure the malignancy. It is equally important to incorporate antiretroviral therapy into the treatment plan. The problem of drug interaction must be expected and thrombocytopenia, a known side effect of zidovudine may pose problems to cancer chemotherapy. The second child in this report was given full dose chemotherapy for the NHL and dual antiretroviral therapy for the HIV infection without much complication. The first child in this report unexpectedly survived almost five years with immuno- and chemoprophylaxis after the initial diagnosis of NHL and AIDS before finally succumbing to lung infection. Although he responded to the anticancer chemotherapy, the course was complicated with numerous severe infections.

One factor contributing to numerous opportunistic infections is prolonged neutropenia commonly associated with treatment of HIV related lymphoma because of the poor bone marrow reserve. To reduce this complication, which arises from haematologic toxicity of anticancer chemotherapy, reduced doses of cytotoxic chemotherapy or standard-dose therapy (m-BACOD) plus myeloid colony stimulating factor has been used[12,13]. It was concluded that reduced doses caused significantly fewer toxic side effect (51% vs 70%, $P = 0.008$) with no reduction in efficacy (median survival 35 weeks vs 31 weeks) compared with standard doses[13].

As the prevalence of HIV infection increases, more cases of HIV infection presenting as NHL will be encountered. Paediatricians now need to consider HIV infection as an underlying cause of childhood cancer, especially NHL. It is recommended that screening for HIV infection be carried out before starting cytotoxic chemotherapy in any childhood NHL and that low-dose chemotherapy should be considered for most HIV-infected patients with lymphoma[12,13].

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