

CASE REPORT

A case report of adult T-cell leukaemia/lymphoma

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Abstract

Adult T-cell leukaemia/lymphoma (ATLL) is a rare T lymphoproliferative disorder which is aetiologically linked with human T-cell lymphotropic virus type-1 (HTLV-1). HTLV-1 is endemic in Japan, Caribbean and Africa. The highest incidence of ATLL is in Japan although sporadic cases have been reported elsewhere in the world. We describe a case of ATLL with an unusual presentation which we believe is the first reported case of ATLL in Malaysia based on our literature search. A 51-year-old Indian lady was referred to University Malaya Medical Centre for an incidental finding of lymphocytosis while being investigated for pallor and giddiness. Clinical examination revealed bilateral shotty cervical lymph nodes with no hepato-splenomegaly or skin lesions. Laboratory investigations showed absolute lymphocytosis ($38 \times 10^9/L$) with a mildly increased serum lactate dehydrogenase. The peripheral blood smear showed the presence of predominantly small to medium sized, non-flower lymphocytes. The bone marrow showed similar findings of prominent lymphocytosis. Immunophenotyping of the bone marrow mononuclear cells showed CD3+, CD4+, CD5+, CD7- and CD25+ which is characteristic of ATLL phenotype. HTLV-1 infection was confirmed by the presence of HTLV-1 proviral DNA in the tumor cells using conventional Polymerase Chain Reaction (PCR) and real-time PCR. Here, we discuss the pathogenesis and characteristics of ATLL as well as the detection of HTLV-1 by real time PCR.

Keywords: Adult T-cell leukaemia/lymphoma, immunophenotyping, real time PCR

INTRODUCTION

Adult T-cell leukaemia/lymphoma (ATLL) is a rare T lymphoproliferative disorder which is aetiologically linked with human T-cell lymphotropic virus type-1 (HTLV-1). HTLV-1 is endemic in Japan, the Caribbean and parts of Africa.¹ ATLL was first described as a distinct clinical entity in Kyoto, Japan in 1977.^{2,3} It occurs in about 5% of asymptomatic carriers of HTLV-1 after a long latency period of more than 30 years.⁴

The clinical picture of ATLL is diverse and can be classified into four categories: acute, lymphoma, chronic and smoldering types.⁵ The smoldering type is described as 5% or more abnormal lymphocytes in the peripheral blood with a normal lymphocyte count, absence of hypercalcaemia, serum lactate dehydrogenase (LDH) levels up to 1.5x the normal upper limit with no lymphadenopathy or organomegaly. Skin and lung lesions may be present. The chronic type is similar to the smoldering type except

for the presence of absolute lymphocytosis with 5% or more abnormal lymphocytes seen in the peripheral blood.

ATLL cells originate from the CD4-positive subset of peripheral T-cells. It is believed that the HTLV-1 provirus becomes clonally integrated in these affected helper T-cells.⁶ The appearance of one or more prevalent T cell clones carrying the HTLV genome represent an increased risk of developing full blown disease.

The highest number of reported cases of ATLL is in Japan although sporadic cases have been reported elsewhere in the world. Here, we describe a case of ATLL with an unusual presentation which we believe is the first reported case of ATLL in Malaysia based on our literature search.

CASE REPORT

A 51-year-old Indian lady was referred to University Malaya Medical Centre for an incidental finding of lymphocytosis while being

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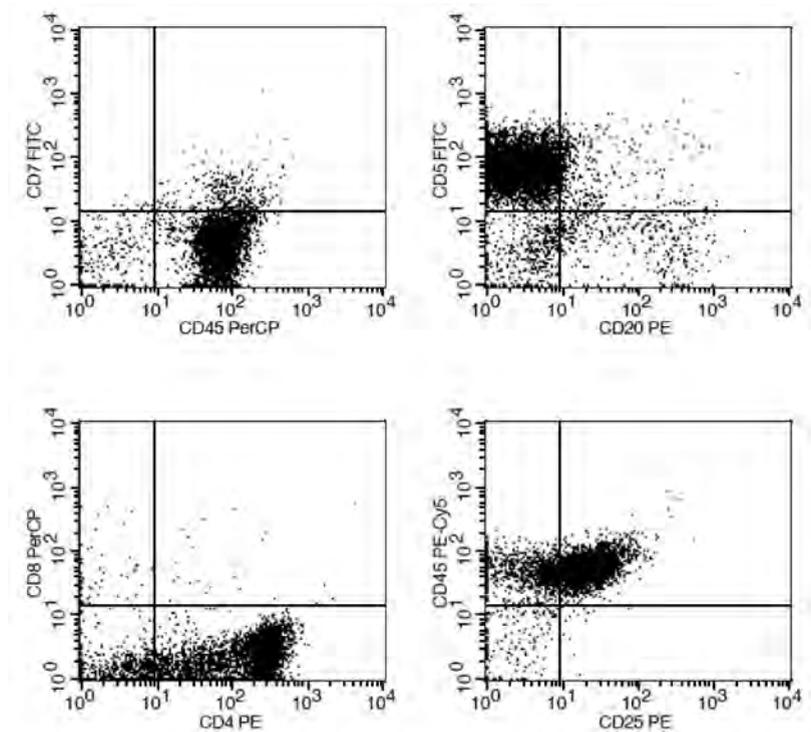


FIG. 1: Flow cytometry scatter plots depicting the abnormal lymphoid cell population which expresses CD7-, CD5+, CD4+ and CD25+.

investigated for pallor and giddiness. She was otherwise well with no significant past medical history and no history of prior blood transfusion. On examination, she was found to be pale with bilateral shotty cervical lymph nodes. There was no hepatosplenomegaly, jaundice or skin lesions noted. Imaging studies confirmed the clinical findings as above and showed ground glass appearance of the lung fields with bilateral lung nodules.

White blood cell count was $42.1 \times 10^9/L$ with absolute lymphocytosis of $38 \times 10^9/L$. Haemoglobin levels was 14.1g/dl and platelet count was $203 \times 10^9/L$. Serum LDH was mildly increased at 216 IU/L. Serum calcium was normal.

The peripheral blood smear showed lymphocytosis with small to medium sized, non-flower lymphocytes. Some of these lymphocytes exhibited nuclear clefting and occasional nuclear convolutions. The bone marrow aspirates and trephine biopsy were hypercellular with predominant lymphocytes. Many of these lymphocytes showed CD3 positivity with immunohistochemical staining. Immunophenotyping demonstrated CD3+, CD4+, CD5+, CD7-, CD8-, CD25+ (dim) and

Tdt- which is characteristic of an ATLL phenotype (Fig. 1). HTLV-1 infection was confirmed by the presence of HTLV-1 proviral DNA in the tumour cells using conventional polymerase chain reaction (PCR) (Fig. 2). Primers used amplified the 159bp segment in the tax region: 5'-CGGATAACCCAGTCTACGTGT-3' and 5'-GAGC CGATAACGCGTCCATCG-3. Real-time PCR was also done at our centre using primers and Taqman probes as previously described⁷ which detected the presence of HTLV-1 pro-viral DNA.

The patient subsequently defaulted follow-up due to unspecified reasons and declined further treatment.

DISCUSSION

ATLL is a mature T-cell neoplasm that occurs in a small percentage of people infected with HTLV-1 predominantly in endemic areas. ATLL has a long latency period and is associated with exposure to the virus very early in life. HTLV-1 is not endemic in Malaysia. Hence, our patient is unique but unfortunately we are unable to elucidate the route of transmission of the virus in her. The main mechanisms of transmission are vertical transmission during pregnancy,

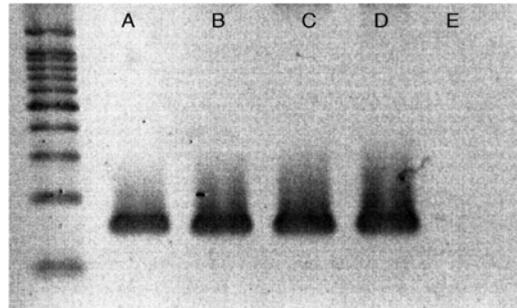


FIG. 2: Gel electrophoresis analysis of amplified DNA for HTLV-1 provirus. Primers used in the PCR reaction amplify 159 bp segment in the tax region of HTLV-1 virus. Lanes A and B are positive controls, Lanes C and D are patient samples and Lane E is the negative control.

breastfeeding, sexual intercourse, blood products transfusion and intravenous drug use.⁶

Several host and viral factors contribute to HTLV-I associated disease pathogenesis such as human leukocyte antigen (HLA) haplotype, viral strain, route of infection and immune response to HTLV-1.⁸ MHC class I molecules that predispose to ATLL are HLA-A*26, HLAB* 4002, HLA-B*4006, and HLA-B*4801. One of the important viral factors is the tax protein encoded by the pX region of the HTLV-1 virus. This protein induces the expression of several cytokines and anti-apoptotic genes which are critical in the proliferation of infected T-lymphocytes.

There are four recognized clinical presentations of ATLL. Of these, the chronic and smouldering forms are relatively indolent whereas the acute and lymphomatous forms are more aggressive. Our patient fits into the chronic subtype⁵ based on her clinical presentation as well as laboratory findings: absolute lymphocytosis, mild lymphadenopathy, presence of abnormal ATLL cells (but no flower cells) with an increased serum LDH.

The diagnosis of ATLL in this patient was initially suspected from the immunophenotyping results which showed an ATLL phenotype although no pathognomonic flower cells were seen in the peripheral blood film. The patient also had no known risk factors for acquiring HTLV-1 infection. This highlights the need for a high index of suspicion for patients with typical immunophenotypic findings of ATLL in areas which are non-endemic for HTLV-1 virus. Detection of HTLV-1 proviral DNA by PCR helped to confirm the diagnosis in this patient. Serological testing for anti-HTLV-1 was not performed.

In conclusion, ATLL is a rare disease in Malaysia and in the absence of classical

morphological findings, the diagnosis of ATLL can be made by characteristic immunophenotyping features and detection of HTLV-1 proviral DNA. Real-time PCR has the advantage over conventional PCR methods because of the shorter turn-around time and can minimize the risk of laboratory contamination. This method can also be used for quantification of HTLV-1 proviral DNA in settings that may require it.

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