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Adult T-cell leukaemia/lymphoma in an adolescent patient: Expect the unexpected

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This case study explores a clinicopathological presentation of Adult T-cell leukaemia/lymphoma (ATLL) at Tygerberg Hospital; a disease associated with adulthood noted in an adolescent patient. Adult T-cell leukaemia–lymphoma oncogenesis develops through a multistep process with an accumulation of mutations. Infection through human T-lymphotropic virus type 1 (HTLV-1) is the first step of a multistep process resulting in eventual clonal proliferation of mature T-cells. There is a long latency period of 20–50 years from the time of infection with HTLV-1 to the development of symptoms of ATLL; thus, ATLL is a malignancy associated with adulthood. The median age of diagnosis is 58, ranging from the third to ninth decade of life. This is an ideal learning case as it highlights the importance of recognising ATLL in children and young adults in our population.

Keywords: ATLL; HTLV-1; T-cell lymphoproliferative neoplasm; flower cells; adolescent.

Introduction

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus that infects different types of cells including T cells, B cells, fibroblasts, dendritic cells and macrophages. Human T-lymphotropic virus type 1 infects regulatory T cells that express CD4, CD25 and FOXP3. Human T-lymphotropic virus type 1-infected T-regulatory cells have a survival advantage over other infected cells because of their ability to suppress the cytotoxic T cells, which normally eradicate HTLV-1 infected cells.[1]

Human T-lymphotropic virus type 1 is endemic in Southern Japan (with a prevalence of 0% – 37%), sub-Saharan Africa (with a prevalence of ≤ 5%), the Caribbean region (with a prevalence of ≤ 6%) and South America (with a prevalence of ≤ 2%).[2,3] In South Africa, the prevalence of HTLV-1 infection among blood donors is < 1%.[4]

Human T-lymphotropic virus type 1 is transmitted through blood transfusion (cellular and/or plasma products), unprotected sex and from mother to baby by vertical transmission. The most efficient mode of HTLV-1 transmission is blood transfusion. Transmission of HTLV-1 by blood transfusion is more commonly associated with myelopathy or tropical spastic paraparesis, while vertical transmission is more commonly associated with the development of Adult T-cell leukaemia/lymphoma (ATLL).[1]

Adult T-cell leukaemia/lymphoma is a rare mature CD4+ T-cell lymphoproliferative neoplasm. The first association between ATLL and HTLV-1 infection was reported in 1982 by Hinuma et al.[5] Only 4% – 7% of HTLV-1-infected people will develop ATLL in their lifetime.[6]

The development of ATLL is a multistep process requiring the accumulation of mutations and epigenetic changes. Human T-lymphotropic virus type 1 infection is the first event in this multistep process which results in clonal CD4+ T cell proliferation.[1,7] There is a long latency period of 20–50 years from the time of HTLV-1 infection to the development of symptoms of ATLL.[1] Given the long latency period, ATLL as the name says is a disease occurring in adulthood with a median age at diagnosis of 58 years and it is extremely rare in childhood.[1,8]

In this article, we present a case of an adolescent with ATLL.

Case report

A 17-year-old female, mixed race patient presented to Tygerberg Hospital with complaints of abdominal pain, nausea, polyuria and weight loss. On examination, the patient was diagnosed with hepatosplenomegaly and an exfoliating rash on her extremities.

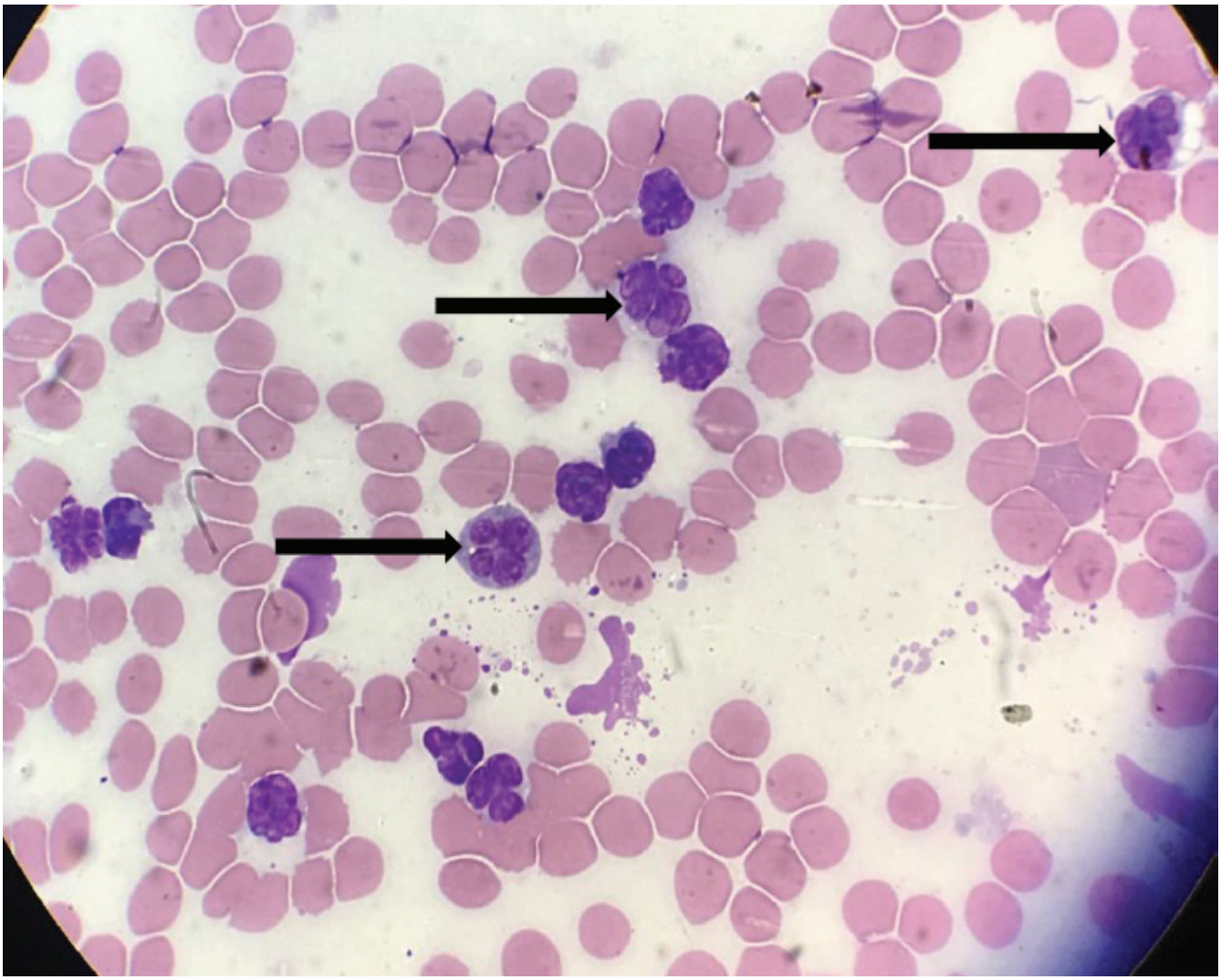

FIGURE 1: Flower cells on peripheral blood (arrows).

A full blood count revealed a leucocytosis count of 286 × 10^9 cells/L. The peripheral blood smear showed lymphocytosis caused by pleomorphic of pleomorphic mature atypical lymphocytes (67%) with cloverleaf or 'flower' nuclei (Figure 1) and absolute eosinophilia (5.9 × 10^9 cells/L). Biochemistry results revealed an elevated lactate dehydrogenase (1269 U/L) and hypercalcaemia (4.82 mmol/L), the latter explaining her presenting symptoms. The test for human immunodeficiency virus (HIV) was negative. The patient had renal impairment with elevated creatinine (143 µmol/L) and urea (15.8 mmol/L) levels.

Flow cytometry showed the characteristic immunophenotype of ATLL: CD2+, CD3+, CD4+, CD8-, CD7- and CD25+. The aberrant loss of CD7 and positive CD25 facilitated the exclusion of Sézary syndrome, which was the main differential diagnosis. The bone marrow was hypercellular with focal infiltration by atypical cells. Karyotyping showed a gain of chromosome 3 (47, XX, +3). Human T-lymphotropic virus type 1 Polymerase Chain Reaction (PCR) was positive. The patient was thus diagnosed with ATLL, an atypical presentation given her age. A positron emission tomography–computed tomography scan (PET-CT) revealed stage IV of the disease and grade IV hydronephrosis of the right kidney secondary to staghorn calculi.

The patient received multi-agent chemotherapy consisting of vincristine, cyclophosphamide and doxorubicin in combination with zidovudine. Bone marrow examination 3 months later showed remission. Positron emission tomography–computed tomography scan 6 months later showed complete remission.

Discussion

The age of onset of ATLL differs across geographical regions; the median age in Japan is 68 years, while in South America it is 40 years.[9,10] The epidemiology of ATLL in Africa is incompletely described. With two other ATLL cases reported in young patients we postulate that there may be a clustering of young ATLL patients in South Africa (unpublished data).

Approximately 1% – 5% of children infected through vertical transmission will develop ATLL.[11] Given the high prevalence of HTLV-1 in pregnant women in Japan (0.6% – 5.8%) compared

to South Africa (0.2%), one would expect higher prevalence of young ATLL cases in Japan compared to South Africa.[12] However, ATLL has not been noted to occur in Japan before the age of 30 years.[10,13] This could be because of the implementation of measures to prevent vertical transmission of HTLV-1 in Japan. These measures include prenatal screening and the avoidance of breast-feeding in women testing positive. Vertical transmission in Japan was reduced from 20.3% to 2.5%.[11]

A study conducted by Bittencourt et al. reported on 24 cases of ATLL in patients aged 18 years and younger. The age at the time of diagnosis in the majority of this cohort (75%, n = 18 cases) was between 11 and 18 years. Sixteen (66.6%) of these were confirmed to be because of vertical transmission of HTLV-1 and one was infected through blood transfusion.[14] In our patient, blood transfusion was excluded. Mother-to-child transmission was the most likely mode of HTLV-1 infection in our patient. The pathogenesis of ATLL in the young is not fully established. Researchers have hypothesised that it is because of the acquisition of HTLV-1 infection at an early age: intrauterine, in the birth canal or during breastfeeding, when the immune system is much less efficient at producing the required T-cell response to HTLV-1 infection.[14]

Several risk factors for the development of ATLL have been proposed.[1,9] Among these risk factors, African ancestry, expansion of T-regulatory cells following multiple types of infections found in low-resource settings, specific human leukocyte antigen (HLA) types and a high rate of vertical transmission because of absence of preventive measures may be contributing factors for the development of ATLL in this patient. Our patient was of mixed ancestry and was not tested for HLA haplotype.

There are four clinical variants of ATLL according to the Shimoyama classification. These are acute, lymphomatous, chronic and smouldering variants and are recognised in the World Health Organisation Classification of Tumours of Haematopoietic and Lymphoid Tissues of 2016 (Table 1).[8,15] The patient described in this case study meets the criteria for the acute subtype.

Clinically, the most commonly involved organs are the skin, lymph nodes, liver and spleen, all which were involved in our patient.[10] The most common presenting symptom in the young population was skin rash.[14] The skin rash is of diverse nature including erythematous rash, papules and nodules with or without ulceration. The chronic variant is typically associated with an exfoliative skin rash.[8] Our patient presented with polyuria, nausea and abdominal pain as a result of hypercalcaemia. Despite fulfilling the diagnostic criteria of the acute variant, our patient had an exfoliative skin rash, which is typically seen with the chronic variant of ATLL.

Adult T-cell leukaemia–lymphoma has a poor prognosis.[15] Reports show that young patients with ATLL generally have a short median survival. In Bittencourt's study, 15 out of the 24 cases (63%) had demised within 6 months of diagnosis.[10]

TABLE 1: Diagnostic criteria for clinical subtypes of adult T-cell leukaemia or lymphoma.

Variable	Smouldering	Chronic	Lymphoma	Acute
Lymphocyte count (×10³/L)	< 4	≥ 4	< 4	High
Flower cells (%)	< 5	≥ 5	≤ 1	High
Lactate dehydrogenase level	≤ 1.5 times ULN	< 2.5 times ULN	High	High
Calcium level	Normal	Normal	High	High
Skin and/or lung involvement	±	±	±	±
Lymph node involvement	No	±	Yes	±
Spleen or liver involvement	No	±	±	±
Central nervous system or bone or pleural or ascites	No	No	±	±

Source: Adapted from Swerdlow SH, Campo E, Harris NL, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2016

ULN, upper limit of normal.

The patient in this case-report had bone marrow involvement which is an independent poor prognostic marker.[16] Despite the poor prognosis, the patient was alive, in complete remission more than a year after diagnosis.

Conclusions

Although ATLL is a disease of adulthood, it may occur in younger patients. The presence of hypercalcaemia, skin rash and suggestive peripheral blood findings should trigger an investigation for ATLL regardless of age. There is a need for a National Registry of ATLL cases in South Africa as such a registry could monitor the trends and offer opportunities for preventive interventions.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

All authors contributed equally to this work.

Ethical considerations

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

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