

Adult T Cell Lymphoma/Leukaemia with Renal Infiltration: A Case Report from Sri Lanka

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1. Abstract

Adult T Cell Leukaemia/Lymphoma (ATLL) is a rare T cell lymphoproliferative disease associated with Human T Cell Lymphotropic Virus-1 (HTLV1) endemic in some parts of the world and therefore has a distinct demographic distribution. There are no cases of ATLL reported in Sri Lanka thus far hence this is the first reported case. Renal parenchymal infiltration in ATLL is extremely rare. Due to the rarity of the disease, evidence-based standard therapeutic options are lacking. The outcome of patients with ATLL is poor, particularly in the relapsed and refractory settings. Here we report a case of ATLL with renal involvement that initially responded to combined chemotherapy but later regressed to refractory disease with poor response to combined immunotherapy and antiviral therapy.

2. Introduction

Adult T Cell Leukaemia/Lymphoma (ATLL) is a highly aggressive T cell neoplasm caused by a retrovirus named Human T Cell Lymphotropic Virus-1 (HTLV-1) which is endemic in Japan, the Caribbean islands, Central and South America, Central and South Africa, a part of the Middle East and Melanesia, and Aboriginal regions in Australia [1]. It is extremely rare in Southeast Asia and there have been no reported cases in Sri Lanka according to our knowledge. It is estimated that approximately 20 million people to be infected by HTLV-1 globally [2]. Over 90% of them remain asymptomatic carriers during their lives and silent transmission

may occur sexually, via breastfeeding, and through blood transfusions [3].

We report a case of an acute subtype ATLL presented with renal infiltration. Due to its rarity in this part of the world, unusual renal parenchymal involvement at presentation, absence of solid treatment guidelines in management, unavailability certain diagnostic tests including serological or molecular tests for HTLV-1 and certain therapeutic options in this resource-restricted setting, we think it is important to report this case.

3. Case Presentation

A 62-year-old lady presented with a history of cervical and axillary lymphadenopathy and intermittent low-grade fever for 3 weeks. There were no skin lesions, unintentional weight loss, excessive night sweats or bleeding manifestations. ECOG performance status (PS) at diagnosis was 1. There was no hepatosplenomegaly. She had hypertension for which she was on multiple antihypertensives and triple vessel disease for which she had undergone coronary artery by-pass graft surgery (CABG) a year ago with normal cardiac functions at baseline. Her renal functions had been previously normal.

Results of some of the important blood investigations at diagnosis are depicted in table 1. There were 25% small to medium sized abnormal lymphoid cells in peripheral blood and the majority of them showed irregular nuclei with nuclear clefts. Serological investigations for CMV, EBV, toxoplasma were negative.

Table 1: Some of the blood investigation results at the diagnosis

Investigation	Value	Normal range
WBC	60.08 x10 ⁹ /L	4 x10 ⁹ /L – 11 x10 ⁹ /L
Neutrophils	52%	40-80%
Lymphocytes	40.60%	20-40%
Haemoglobin	10.6 g/dL	11.8-14.8%
Platelets	223x10 ⁹ /L	150 x10 ⁹ /L – 400 x10 ⁹ /L
Serum Albumin	3.7g/L	35-50 g/L
ESR	50 mm/1 st hour	<20mm/1 st hour
CRP	16.4 mg/L	<6 mg/L
LDH	1210 IU/L	225-450 IU/L
β2 microglobulin	2.9 μg/L	1.2-2.7 μg/L
Serum ionized calcium	4.8 mg/dL	4.6-5.2 mg/dL
Serum creatinine	3.6 mg/dL	0.5-0.9 mg/dL
eGFR	20 ml/min/1.73m ²	>90 ml/min/1.73m ²

Bone marrow aspirate revealed a population of small to medium sized lymphoid cell with irregular and clefted nuclei representing 50% cells. Cytoplasmic blebs were also noted in some of these cells. There were no central nucleoli. Flowcytometry gated 25% of cells at high CD45 region in CD45/SSC out of which 90% were CD3 positive T lymphocytes and 5% CD19 positive B lymphocytes. CD3 positive cell population was negative for CD4, CD7, CD8, CD19, CD94, CD99, HLADR, CD56, CD16, CD30, CD 7 and MPO and was positive for CD 2, CD5 and T-cell receptor αβ while a subset of cells was CD 10 positive. CD 25 was diffusely and strongly positive (Figure 1). Fluorescent in situ Hybridization (FISH) detected T cell rearrangements (TCRA/D 14q11).

Left axillary lymph node excision biopsy revealed effaced nodal

architecture with a diffuse infiltrate of monomorphic small, mature lymphoid cells. They showed condensed chromatin and irregular nuclear contours. A few scattered medium sized cells and plasmacytoid cells were also seen. There was marked dilatation of sinuses and prominent high endothelial proliferation infiltrated with atypical lymphocytes. Perinodal spread of atypical lymphocytes was also noted. Immunohistochemistry revealed diffuse, strong positivity of atypical lymphocytes for CD3 (membrane and cytoplasmic) and CD5. These cells were weakly positive for CD30 and BCL 2. Atypical lymphoid cells were negative for CD7, CD20, CD23, Tdt, CD34, CD15, ALK-1 and S-100. Ki-67 proliferative index was around 35%. CD20 highlighted the residual lymphoid follicles.

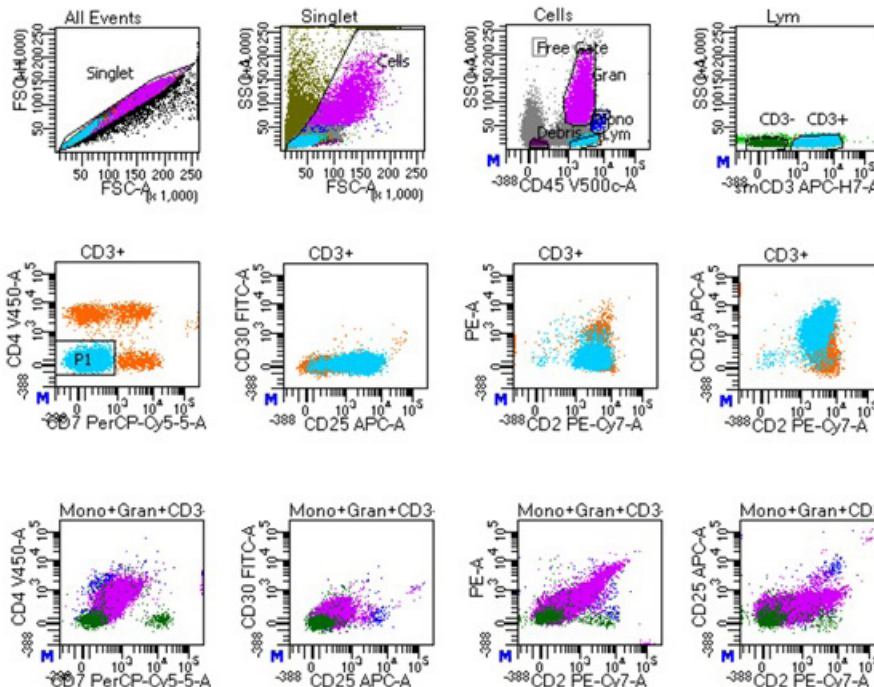


Figure 1: Peripheral blood flowcytometry showing the CD3+ CD25+ abnormal T cell population

The clinical manifestations and cytology fit in with the diagnosis of ATLL. When the immune profile was considered, it lacked CD4 expression which was unusual for ATLL. However, strong expression of CD25 is a sensitive marker with absence of CD 7 suggestive of ATLL. Detection of HTLV-1 with serology as well as PCR

confirmed the diagnosis.

Positron Emission Tomography (PET) scan showed a left level I, II and IV and right level V lymphadenopathy ranging in size from 0.8cm to 1.12cm and in maximum Standard Uptake Value (SUV-max) from 3.55 to 4.26. In left axilla, the largest metabolically ac-

tive node measured 2.28cm with an SUVmax of 4.38. There were para-aortic and bilateral inguinal lymph nodes ranging from 0.7 to 1.2 cm in size and 4.5 to 7.5 in SUVmax. The skeleton as well as the renal parenchyma showed diffusely increased metabolic activity with SUVmax of 8.66 in the right kidney and 9.2 in the left (Figure 2). Renal biopsy was not performed but the convincing radiological evidence with renal impairment was suggestive of lymphoid infiltration of the kidneys.

The patient was started on IV hydration and steroids after the biopsies and blood investigations. Once the diagnosis was suggested by immunophenotyping, she was given one cycle of CVP (Cyclophosphamide, Vincristine, Prednisolone) chemotherapy and doses were adjusted according to the renal function. There was an initial response to chemotherapy with normalisation of peripheral blood

counts and renal functions. Subsequently, with the confirmation of the diagnosis, she was started on CHOEP chemotherapy. (Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisolone) HLA typing was done of the patient and the siblings in view of a prospective allogeneic transplant on achieving a complete remission. She developed neutropenic sepsis with the 2nd cycle of chemotherapy and was treated with broad spectrum IV antibiotics. After the 4th cycle of chemotherapy, bone marrow biopsy was repeated to assess the response which showed residual disease. She was offered Interferon α 2b and Zidovudine at this point. Sadly, the patient developed severe renal impairment with progressive disease not responding to antivirals and immunotherapy. The CT scan of the chest showed diffuse parenchymal pulmonary infiltrates and the patient succumbed to refractory disease leading to multiorgan failure and sepsis with opportunistic infections.

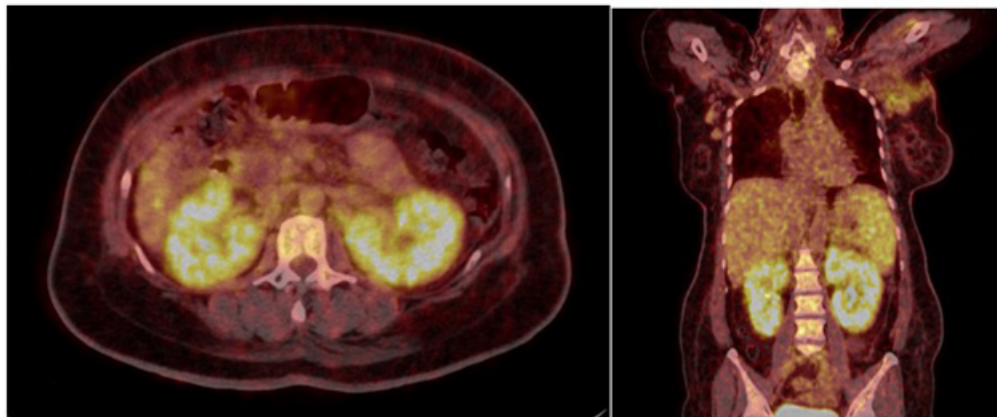


Figure 2: PET scan showing renal infiltration, left axillary and cervical lymph node involvement

4. Discussion

Based on the Shimoyama criteria, ATLL is classified into four categories based on organ involvement, lactate dehydrogenase (LDH) and calcium values, namely, chronic (5%), smouldering (15%), lymphoma (20%) and acute (60%) [4]. According to these criteria, our patient belonged to the acute subtype. Diagnosis is based on clinical features, morphological and immunophenotyping characteristics of the abnormal lymphoid population and evidence of HTLV-1 infection. The latter is not available in Sri Lanka and peripheral blood samples were sent to India for serology and PCR. ATLL is characterized by the clonal expansion of mature activated T cells generally CD3+ CD4+ CD5+ CD7- CD8- CD25+ [5]. However, the present case was unusually CD4 negative but was strongly positive for CD25.

The acute form of ATLL is the most aggressive, characterized by marked leucocytosis with atypical lymphocytes, skin lesions (erythematous rash, nodules or papules), constitutional symptoms, hepatosplenomegaly and massive lymphadenopathy that spare mediastinum [6]. Hypercalcemia and elevated LDH are frequently present. While, the index case showed severe leucocytosis with nearly $15 \times 10^9/L$ atypical lymphoid cells in peripheral blood, raised LDH which was more than 3 times the upper limit of normal range

and lymphadenopathy sparing mediastinum although not massive, she did not have any skin manifestations, hypercalcaemia or hepatosplenomegaly. Lymph nodes, skin, liver, spleen, lung, GI tract, bone marrow, bone, and CNS are the frequent sites involved in ATLL [7]. In our patient, lymph nodes and bone marrow were involved. The PET scan showed bilateral renal parenchymal infiltration with renal impairment at presentation. Although lymphomatous infiltration of renal parenchyma is not uncommon with B-cell lymphomas, only a few reports of infiltration of T-cell lymphomas with renal infiltration exist in the literature. Renal involvement with ATLL is reported extremely rarely [8].

The survival rate varies depending on the subtype, with 4 to 6 months for the acute variant [4]. A multivariate analysis of 854 patients identified advanced performance status, elevated LDH level and β 2-microglobulin, age above 40 years, presence of more than three involved lesions and hypercalcemia to be associated with shortened survival [9]. In addition, thrombocytopenia, eosinophilia, bone marrow involvement, high interleukin-5 serum level, C-C chemokine receptor 4 expression, lung resistance-related protein, p53 mutation, and p16 deletion have also been shown to fare poor prognosis [7]. Our patient clearly had poor prognostic factors.

The current guidelines for management of ATLL has been published in 2009 by the International Consensus Meeting of the American Society of Clinical Oncology [7]. It has been suggested to treat acute aggressive variants with poor prognostic factors with chemotherapy followed by myeloablative or reduced-intensity allogeneic haematopoietic stem cell transplantation (allo-HSCT). Chemotherapy regimens, such as the modified LSG15 regimen, consists of six cycles of vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) which has shown a 3-year survival rate of 24%, a complete response rate (CRR) of 40%, and a median survival time (MST) of 13 months in 118 previously untreated patients with aggressive ATLL [10]. However, vindesine and ranimustine are not available in Sri Lanka. Considering the comorbidities, PS and age it was not thought that the patient would tolerate such intensive regimens as VCAP-AMP-VECP. Therefore, CHOEP was started with the intention of sending the patient to Singapore for a reduced intensity conditioning allo-HSCT. Renal functions were normalised and lymphadenopathy clinically disappeared with the first cycle of chemotherapy.

Allo-HSCT is considered a promising treatment of young patients with aggressive ATLL. Despite high treatment related mortality in a retrospective multicenter analysis, the estimated 3-year OS rate of 45% is promising, possibly reflecting a graft-versus leukaemia effect [11]. However, the index case was not the ideal candidate for allogeneic stem cell transplantation due to the poor performance status, comorbidities and most importantly, refractory disease which was evident after the fourth cycle of chemotherapy.

Numerous small phase II trials using Zidovudine (AZT) and Interferon- α have shown promising responses in ATLL patients [7]. High-doses of both agents are recommended (6 to 9 million units of Interferon- α in combination with daily divided AZT doses of 800 to 1,000 mg/d) [12]. A meta-analysis showed a 5-year OS rate of 46% with first-line antiviral therapy and 20% with first-line chemotherapy [13]. This patient was also started on AZT and Interferon- α due to refractory disease. However, disease was rapidly progressive leading to pulmonary and renal involvement. Aggressive forms of ATLL are inherently associated with an intrinsic chemo-resistance and secondary opportunistic infections due to profound immunosuppression [4]. Unfortunately, our patient also developed disseminated opportunistic infections leading to severe sepsis and ARDS in the background of progressive acute renal failure and she succumbed to death due to multi organ failure.

5. Conclusions

ATLL is a rare T cell lymphoproliferative malignancy with a spectrum of clinical manifestations and is extremely rare in Sri Lanka. Clinical, morphological, immunophenotypical, serological and genetic information is vital in establishing the diagnosis but can

be extremely challenging in this resource-restricted setting. The aggressive acute variant of ATLL has a dismal prognosis with disappointing results with combined chemotherapy regimens and remains an unmet clinical need with no satisfying therapy at present.

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