ECRONICON OPEN ACCESS

EC MICROBIOLOGY
Review Article

T-cell Leukemia: Presentation and Management

Amal Mohammed Albeihany[1]*, Mohammed Talal Alyami[2], Khaled Fayez Alahmadi[2], Qusai Sami Abdulghani[2], Athir Athallah AlRuwaili[3], Gharam Moghdeb AlRuwaili[3], Afaf Matar Alshamari[3], Abeer Zaid Almazyad[3], Muhjah Abdulhakim Bukhari[4], Rahaf Abdulmoniem Alhujili[4] and Khalid Mnawer Almutairi[5]

[1]*Consultant Hematologist and Bone Marrow Transplant, King Fahad Hospital, Medina, Saudi Arabia*

[2]*Taibah University, Medina, Saudi Arabia*

[3]*Aljouf University, Aljouf, Saudi Arabia*

[4]*Umm Al-Qura University, Mecca, Saudi Arabia*

[5]*Almeeqat General Hospital, Al Madinah, Saudi Arabia*

***Corresponding Author:** Amal Mohammed Albeihany, Consultant Hematologist and Bone Marrow Transplant, King Fahad Hospital, Medina, Saudi Arabia.

Received: September 17, 2019; **Published:** September 24, 2019

Abstract

Introduction: Leukemia is a cancer of blood and bone marrow. The blood cells divide and grow continuously due any damage to DNA leading to leukemia. T-cell leukemia can be classified as adult T-cell lymphoma/leukemia (ALT), large granular lymphocytic leukemia (LGLL) and prolymphocytic leukemia (PLL). Adult T-cell leukemia is rare and aggressive lymphoproliferative neoplasm caused by human T-cell lymphotropic virus type 1 (HTLV-1) and has a poor prognosis. Various forms have been recognized with different clinical course and prognosis. Organomegaly, skin involvement, atypical lymphocytes (flower cells) with CD4+ CD25+ phenotype and hypercalcemia are some common features of disease. Diagnosis should be based on clinical features and laboratory investigation. Anti-retroviral agents in combination with alpha-interferon, without concomitant chemotherapy have shown improvement in survival rates. Standard treatment options are lacking; thus, outcomes are unsatisfactory, especially in case of patients with relapsed and refractory disease.

Aim of the Study: The review helps us to understand the pathogenesis, clinical presentation, diagnosis, and recent advancement in treatment of T-cell leukemia.

Methodology: The review is a comprehensive Search of PUBMED, and Google Scholar search engine since the year 1991 to 2018.

Conclusion: Significant progress has been made in understanding the pathogenesis and clinical characteristics of T-cell leukemia and in the treatment options accordingly. However, the prognosis remains poor for most of leukemia. Various treatments have been studied and are commercially available. In this way emerging therapies with novel mechanism of action, therapies which aim to increase immune response and targeting different pathways may further expand the number of available treatment options and thus improve the outcome.

Keywords: *Adult T-Cell Leukemia; Chemotherapy; Hematological Picture; Treatment*

Introduction

Adult T-cell leukemia/lymphoma (ATL) is mature T-lymphoid malignancy of T-lymphocytes CD4+ CD25+ (post-thymic pleomorphic activated). Its aetiologically associated with the human T-cell lymphotropic virus, HTLV-I and this makes it a distinct entity in WHO

classification [1]. The prevalence of ATL occurs in endemic regions, such as southern Japan, the Caribbean, central and south America, intertropical Africa, Romania, and northern Iran. HTLV-I causes transformation and clonal expansion of T-cells in approximately 1 - 4% of estimated 10-20 million infected hosts, with mean latency period of more than 50 years [2-4].

Methodology

We did a systematic search for management and presentation of T-cell leukemia using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Adult T-cell leukemia, chemotherapy, hematological picture, treatment.

Pathogenesis

The serum of ATL patients contain antibodies to HTLV-I, and the provirus is clonally integrated into most of the CD4+ and CD25+ activated T-lymphocytes, also known as leukemic flower cells which are characteristic of ATL. The exact mechanism of leukemogenesis is not known. However, the HTLV-I infection is found to be the first event of multistep oncogenic process [5]. The oligoclonal expansion of virus-infected T-cells results from expression of viral trans-activator protein Tax, which in turn activate the viral promoter and various cellular gens and create an autocrine loop involving IL-2, IL-15 and their cognate receptors. Tax changes cellular pathways such as activation of cAMP response element-binding protein or cAMP-dependent transcription factor, adaptor-related protein complex 1 and NF-kB, upregulation of anti-apoptotic proteins, repression of p53, DNA polymerase-beta, proliferating cell nuclear antigen, mitotic spindle assembly checkpoint protein MAD1 and disruption of various cell-cycle regulators, including cyclins and inhibitor of cyclin-dependent kinases [6-9].

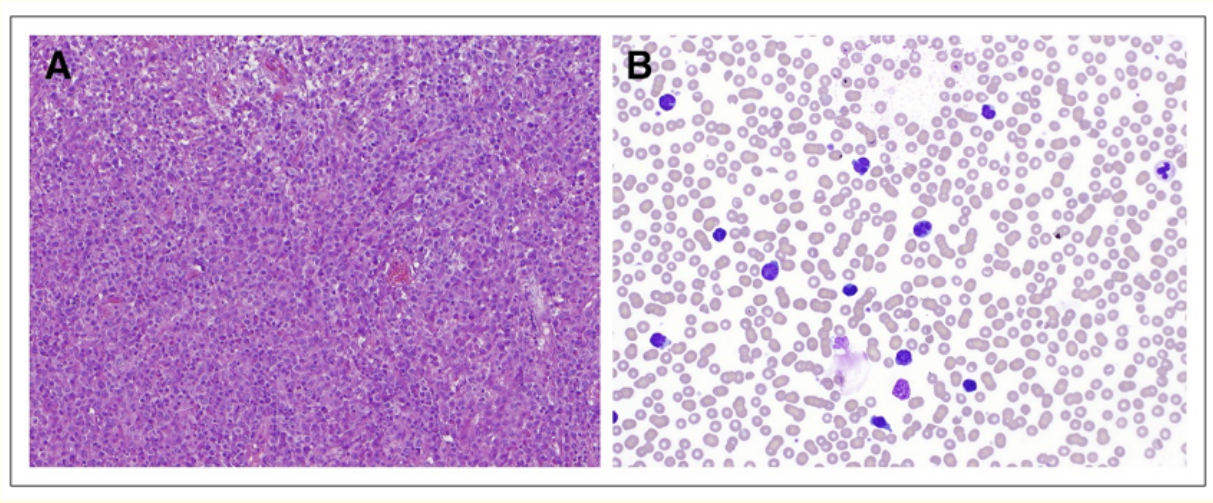

Figure 1: *(A) Lymph node biopsy (B) Peripheral smear in adult T-cell lymphoma/leukemia (ATL) showing neoplastic cells characteristically have a flower-like or clove shaped appearance [10].*

A minimum of 5% of circulating abnormal T-lymphocytes are required to diagnose ATL in patients without histologically proven tumor lesions. These cells express the surface-cell lymphocytic markers CD2, CD4, CD5, CD45Ro, CD29 and T-cell receptor (TCR) αβ and are mostly negative for CD7, CD8 and CD26 show reduced CD3 expression [10].

Clinical presentation

ATL exclusively affects adults, and in some rare case children. The median age is found to be around mid-60s with no gender prevalence. The familial trait has been reported in Japan, USA, and England. ATL may co-exist with other HTLV-I induced diseases such as tropical paraparesis [11].

Clinical Forms	Features
Acute	Organomegaly, high lactate dehydrogenase (LDH), hypercalcemia, Leukemic picture.
Chronic	Lymphocytosis with ATL cells, the involvement of skin, lung, liver, node.
Smoldering	Skin and lung infiltrates, no other organ involvement, normal lymphocyte count (1 - 5% ATL cells), normal level of calcium and LDH
Lymphoma	Organomegaly, circulating leukemic cell less than 1%, high LDH, and possible hypercalcemia.

Table 1: *Based on disease manifestation, classification of ATL [11].*

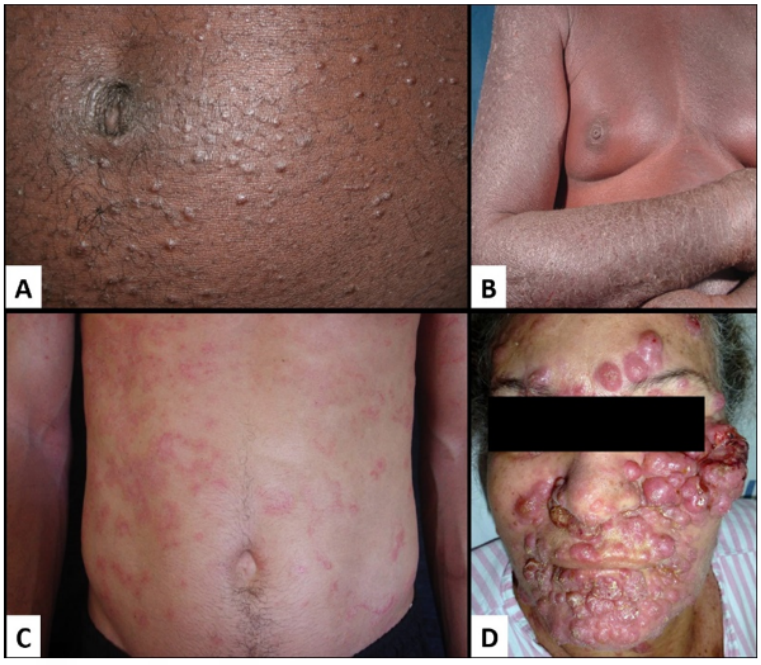

Figure 2: *Cutaneous lesion observed in ATL (A) chronic form with popular pattern (B) Acute form showing exfoliative erythroderma (C) smoldering form with pattern of papules and erythematous scaly plaques. (D) primary cutaneous tumoral form [12].*

Among all the clinical forms the most common presentation is acute, seen in around 65% of patients, characterized by the presence of systemic symptoms, organomegaly, lymphadenopathy, and leukemic picture. Lytic bone lesions may or may not be present. Half of the patients present with skin lesions. The lymphocytosis in chronic form may remain stable for months along with skin manifestation. The smoldering way is usually asymptomatic or manifest as skin rashes with less than 3% of atypical circulating lymphocytes. Less than

a third of patient present with lymphoma and no evidence of blood involvement. The disease progression to acute from chronic and smoldering form is seen [11].

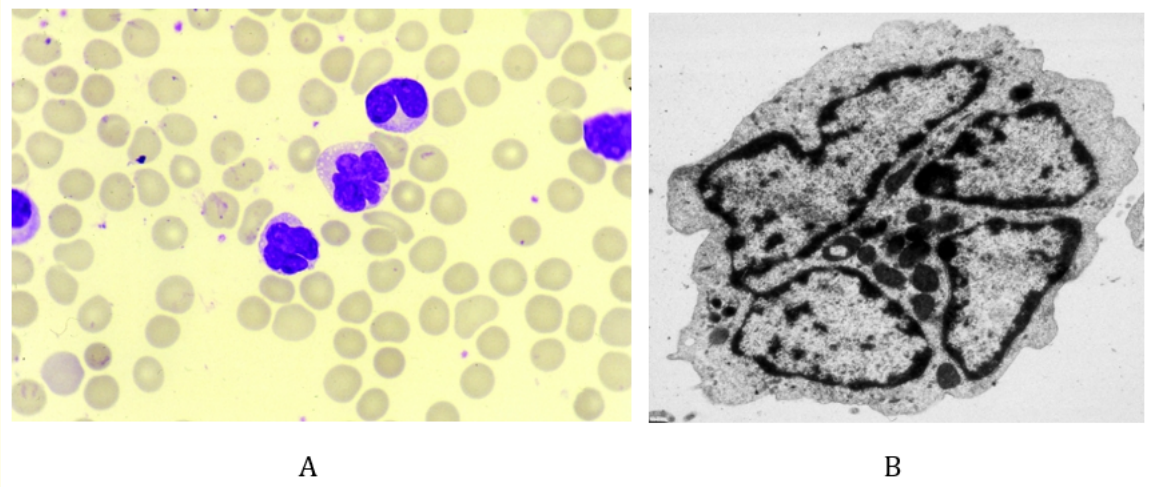

Figure 3: *(A) Circulating lymphocytes showing a convoluted polylobated nucleus. (B) Electron micrograph of an adult T-cell leukemia/lymphoma cell, showing a nucleus integrated by different segments. Uranyl acetate and lead nitrate stain [11].*

The other symptoms are related to neoplastic conditions such as immunocompromised status of the patients, which prone them to develop opportunistic infections that complicate the course of the disease and makes the management even more difficult than usual. The infestation of Strongyloides stercoralis may be severe and fatal [11].

Diagnosis and haematological picture

Peripheral blood

WBCs are raised in acute and chronic form. The peripheral blood picture shows anemia and thrombocytopenia, neutrophilia and eosinophilia. The cytological picture is pleomorphic showing medium-sized lymphocytes with condensed chromatic and convoluted or polylobated nucleus characteristic "flower cell." The cytoplasm is scanty and agranular with variable degree of basophilia along with presence of few blast cells [11].

Bone marrow

The bone marrow aspirate shows infiltration by lymphocytes with similar morphological features seen in blood. The infiltration may be very subtle or patchy and ranges from interstitial to diffuse. Presence of increased osteoclast with bone resorption which lead to hypercalcemia [11].

Lymph node and other tissue

The infiltration to lymph node is often diffuse with paracortical area expanded by infiltrating of lymphocytes of various sizes and nuclear shapes. There may be presence of immunoblast like and Reed-Sternberg like cells, histological pattern resembling Hodgkin disease.

Thus, the lymph node histology of ATL is not clear and distinctive and almost indistinguishable from other peripheral T-cell lymphoma. The skin histology shows lymphoid infiltrates in the dermis, epidermotropism is present forming pautrier's micro abscesses [13].

Immunophenotype

It is that of an activated mature T-lymphocyte. The cells usually express CD2 and CD5 and are mostly negative for CD7, CD3 and TCR-beta may be down-regulated. The most characteristic immunophenotypic feature of neoplastic cell is strong expression of alpha chain of IL-2 receptor recognized by monoclonal antibody CD25. Although such expression is distinctive but not unique to ATL [13].

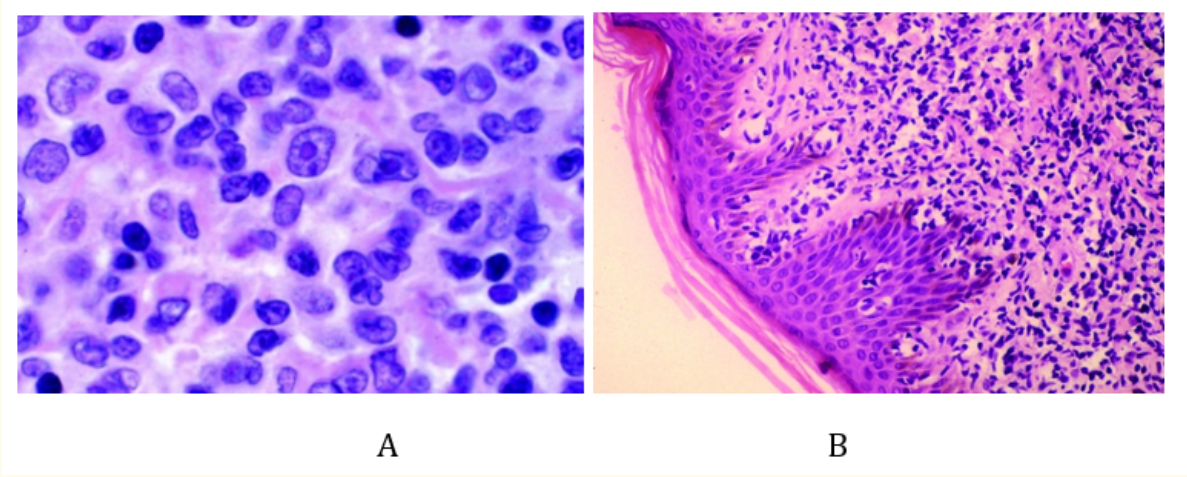

Figure 4: *(A) Section of lymph node showing infiltration of lymphoid cells and cytological pleomorphism. (B) Skin biopsy showing dermal infiltrate with epidermotropism and Pautrier's micro abscesses [11].*

Cytogenetic and molecular biology

The cytogenetic analysis shows a complex karyotype. Recurrent abnormalities of +3, +&, +21, monosomy X, deletion of chromosome Y and abnormalities of chromosome 6 and 14q.The molecular analysis is helpful mostly in cases with acute and lymphoma form. It shows mutation of tumor-suppressor genes CDKNA2A (p16), CDKN2B (p15) and TP53 (p53) [14].

Thus, the diagnosis of ATL is established by reviewing clinical and laboratory features. The hematological picture of circulating neoplastic lymphocytes are essential in establishing the diagnosis. Histology of lymph node, in particular, is not required in whom cytology and immunophenotyping are typical of disease and in whom serum antibodies to HTLV-I are demonstrable. However, diagnosis of lymphomatous form is more difficult as its histological features are very similar to that of other lymphomas. HTLV-I is mandatory investigation [14].

Treatment

Conventional chemotherapy

Chemotherapy provides limited long-term efficacy, yet the cytotoxic combination chemotherapy remains the mainstay for the treatment of ATL. The clinical trial from japan uses regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) or aggressive chemotherapy VCAP-AMP-VCEP (vincristine, cyclophosphamide, doxorubicin and prednisone; doxorubicin, ranimustine, and prednisone; and vindesine, etoposide, carboplatin, and prednisone) for chronic, lymphoma and acute subtypes. This initial therapy

provides response of up to 70%. EPOCH (etoposide, prednisolone, vincristine, cyclophosphamide, and doxorubicin) has also been tried for ATL. According to a study; using dose-adjusted EPOCH in 3637 together with interferon and zidovudine, showed overall response rate of 58% with two complete remissions [15-17].

HSC transplantation

Despite the aggressive first-line approaches, 90% of patients experience relapse within months of completing therapy, in this case first remission with allogeneic stem-cell transplantation is considered. According to a retrospective series, the donor HTLV-I seropositivity adversely affected the disease-associated mortality and given a typical acquisition of virus from the mother, often difficult to find matched siblings unaffected with virus. Autologous stem-cell transplantation doesn't seem to provide effect in managing ATL [18-20].

Monoclonal antibodies

Monoclonal antibodies against IL-2 receptor have been used in patients with relapsed and refractory ATL. Alemtuzumab has demonstrated good results against CD52 but to a limited case. Mogamulizumab, defucosylated, humanized monoclonal antibody target CCR4. This in combination with dose-intensified chemotherapy has also proven to be efficient [18].

Anti-retroviral therapy

Role of antiretroviral therapy remains controversial. Zidovudine is the most studied antiviral used for ALT and Zidovudine in combination with interferon showed a promising result. While according to some studies raltegrevir and lamivudine have proven to be beneficial [17,21].

In addition to these the current landscape for treatment include various other agents such as [22]:

- Antimetabolites- Cladribine, Clofarabine, Pralatrexate.
- Protease inhibitor- Bortezomib.
- Aurora A kinase inhibitor- Alisertib.
- Immunomodulatory agent- Lenalidomide.
- Therapeutic vaccine- The tax peptide-pulsed dendritic cell (Tax-DC) vaccine.

Conclusion

Despite the advances in knowledge of molecular biology, oncogenic mechanism involved in ATL, multiagent chemotherapeutic approaches, the prognosis remains poor; especially the acute and lymphoma form. Diagnosis is usually made with typical hematology picture and clinical symptoms, but choice of treatment remains controversial. However, the best results are achieved with combination therapy of antiretroviral drugs, interferon and chemotherapy. Non chemotherapeutic agents such as mogamulizumab and stem-cell transplantation in young patient has proven to increase the survival rate.

Bibliography

1. Kikuchi M. "Adult T cell leukaemia/lymphoma". Pathology and Genetics of Tumours Haematopoietic and Lymphoid Tissues (2001): 200-203.

2. Kaplan JE and Khabbaz RF. "The epidemiology of human T-lymphotropic virus types I and II". *Reviews in Medical Virology* 3.3 (1993): 137-148.

3. Gessain A. "Epidemiology of HTLV-I and associated diseases". Human T-cell lymphotropic virus type 1 (1996): 33-64.

4. Franchini G. "Disease association, genetics, and biology of human T-cell lymphotropic virus types I and II". *Blood* 96 (2002): 409-411.

5. Franchini G. "Molecular mechanisms of human T-cell leukemia/lymphotropic virus type I infection". *Blood* 86.10 (1995): 3619-3639.

6. Wattel E., *et al*. "Clonal expansion of human T-cell leukemia virus type I-infected cells in asymptomatic and symptomatic carriers without malignancy". *Journal of Virology* 69.5 (1995): 2863-2868.

7. Azimi N., *et al*. "Involvement of IL-15 in the pathogenesis of human T lymphotropic virus type I-associated myelopathy/tropical spastic paraparesis: implications for therapy with a monoclonal antibody directed to the IL-2/15Rβ receptor". *The Journal of Immunology* 163.7 (1999): 4064-4072.

8. Yoshida M. "Multiple viral strategies of HTLV-1 for dysregulation of cell growth control". *Annual Review of Immunology* 19.1 (2001): 475-496.

9. Matsuoka M and Jeang K T. "Human T-cell leukaemia virus type 1 (HTLV-1) infectivity and cellular transformation". *Nature Reviews Cancer* 7.4 (2007): 270-280.

10. Mehta-Shah N., *et al*. "Adult T-cell leukemia/lymphoma". *Journal of Oncology Practice* 13.8 (2017): 487-492.

11. Matutes E. "Adult T-cell leukaemia/lymphoma". *Journal of Clinical Pathology* 60.12 (2007): 1373-1377.

12. Oliveira PD., *et al*. "Adult T-cell leukemia/lymphoma". *Revista da Associação Médica Brasileira* 62.7 (2016): 691-700.

13. Ohshima KI., *et al*. "Lymph nodes in incipient adult T-cell leukemia-lymphoma with Hodgkin's disease-like histologic features". *Cancer* 67.6 (1991): 1622-1628.

14. Yamaguchi K. "Human T-lymphotropic virus type I in Japan". *The Lancet* 343.8891 (1994): 213-216.

15. Phillips AA., *et al*. "A critical analysis of prognostic factors in North American patients with human T-cell lymphotropic virus type-1-associated adult T-cell leukemia/lymphoma: A multicenter clinicopathologic experience and new prognostic score". *Cancer* 116.14 (2010): 3438-3446.

16. Suzumiya J., *et al*. "The International Prognostic Index predicts outcome in aggressive adult T-cell leukemia/lymphoma: analysis of 126 patients from the International Peripheral T-Cell Lymphoma Project". *Annals of Oncology* 20.4 (2009): 715-721.

17. Ratner L., *et al*. "Human T cell leukemia virus reactivation with progression of adult T-cell leukemia-lymphoma". *PLoS One* 4.2 (2009): e4420.

18. Bazarbachi A., *et al*. "How I treat adult T-cell leukemia/lymphoma". *Blood* 118.7 (2011): 1736-1745.

19. Hishizawa M., *et al*. "Transplantation of allogeneic hematopoietic stem cells for adult T-cell leukemia: a nationwide retrospective study". *Blood* 116.8 (2010): 1369-1376.

20. Phillips AA., *et al*. "A multi-institutional experience of autologous stem cell transplantation in North American patients with human T-cell lymphotropic virus type-1 adult T-cell leukemia/lymphoma suggests ineffective salvage of relapsed patients". *Leukemia and Lymphoma* 50.6 (2009): 1039-1042.

21. White JD., *et al*. "The Combination of Zidovudine and Interferon AIpha-2B in the Treatment of Adult T-Cell Leukemia/Lymphoma". *Leukemia and Lymphoma* 40.3-4 (2001): 287-294.

22. Hermine O., *et al*. "A review of new findings in adult t-cell leukemia-lymphoma: A focus on current and emerging treatment strategies". *Advances in Therapy* 35.2 (2018): 135-152.

Volume 15 Issue 10 October 2019