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Original Article - Case Report

Rare Presentation of Adult T-cell Leukaemia/Lymphoma Mimicking Hodgkin Lymphoma: A Case Report

*Poorva Gurjar [1], Nilay Nishith [1], Sankalp Sancheti [1], Dr. Puneet Somal [1], Aishwarya Sharma [1], Gunit Nongthombam [1], Ravikiran N Pawar [1,] *, Pooja Prasad [2]*

[1] Department of Oncopathology, Homi Bhabha Cancer Hospital and Research Centre, New Chandigarh, India
[2] Department of Medical Oncology, Homi Bhabha Cancer Hospital and Research Centre, New Chandigarh, India

* *Corresponding author*: *Dr. Ravikiran N. Pawar*, Department of Oncopathology, Homi Bhabha Cancer Hospital and Research Centre, New Chandigarh, India; Email: ravikiransingh2512@gmail.com

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ABSTRACT

Adult T-cell leukaemia/lymphoma (ATLL) is a mature T-cell neoplasm associated withhuman T-lymphotropic virustype 1 (HTLV-1) infection and guarded prognosis.'Hodgkin-like' is a rare morphological variant of ATLL, which represents the incipient neoplastic phase of ATLL and follows an indolent clinical course as compared to typical ATLL. However, the management approach, treatment and prognosis of conventional "Hodgkin-like' variant varies from that of Hodgkin lymphoma. Hence, it is important to distinguish between these two entities and to test for HTLV-1 infection in all cases of T-cell lymphoma showing features of ATLL and in those with features of classic Hodgkin lymphoma where the background lymphoid cells (other than the HRS-like cells) appear atypical. A multidisciplinary approach including the correlation of peripheral blood picture with immunophenotyping along with LN biopsy and immunohistochemistry is beneficial for the correct diagnosis of T cell lymphomas with morphological variations. Hereby we describe a rare case of ATLL with Hodgkin-like cells mimicking Hodgkin lymphoma. This is important to distinguish those due to difference in the treatment and outcome.

Keywords

Hodgkin-like ATLL, T cell chronic lymphoproliferative neoplasm, Hodgkin lymphoma.

Abbreviations

Adult T-cell leukaemia/lymphoma (ATLL); Classic Hodgkin Lymphoma (CHL); Hodgkin lymphoma (HL); human T-lymphotropic virustype 1 (HTLV-1); HTLV-1 basic leucine zipper factor (HBZ-ISH); lymph nodes (LN); Reed Sternberg-like (RS-like); Treatment schemes: ATL-G-CSF (vincristine, vindesine, doxorubicin, mitoxantrone, cyclophosphamide, etoposide, ranimustine, and prednisolone with prophylactic support by granulocyte-colony stimulating factor); ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); BEACOPP (dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone); CHOP21 (cyclophosphamide, doxorubicin, vincristine, and prednisolone); mEPOCH (etoposide, prednisolone, vincristine, carboplatin, and doxorubicin; carboplatin was substituted for cyclophosphamide); VCAP-AMP-VECP (a sequential combination chemotherapy consisting of vincristine, cyclophosphamide, doxorubicin, and prednisolone; doxorubicin, ranimustine, and prednisolone; and vindesine, etoposide, carboplatin, and prednisolone).

INTRODUCTION

Adult T-cell leukaemia/lymphoma (ATLL) is a mature T-cell neoplasm associated with retrovirus human T-lymphotropic virus type 1 (HTLV-1) infection and is classified under the category of Mature T-cell and NK-cell neoplasms according to the fifth edition of World Health Organization classification of Haemato-lymphoid Tumours, 2022 as well as the International Consensus Classification of Mature Lymphoid Neoplasms, 2022. It carries one of poorest prognoses among all the non-Hodgkin lymphomas. Around 3-5% of patients with HTLV-1 infection are reported to develop ATLL, for which the associated risk factors described are male sex, older age, higher HTLV-1 proviral load (≥ 40 copies per 1000 peripheral blood mononuclear cells), longer duration of infection (> 20 years), and younger age at acquisition (infancy or childhood) [1].

Patients with ATLL present with varied clinical features such as generalized lymphadenopathy, skin lesions in approximately half of the patients, hepatosplenomegaly, signs and symptoms related to other organ infiltration. The disease is typically classified in four subtypes, based on the clinical presentation and course: acute, lymphoma, chronic, smoldering [2].

'Hodgkin-like' is a rare morphological variant of ATLL, which represents the incipient neoplastic phase of ATLL and follows an indolent clinical course as compared to typical ATLL [3,4]. The pathogenesis of conventional 'Hodgkin-like' variant of ATLL is thought to involve a combination of EBV-infected polyclonal B cells mimicking HRS-like cells and clonal HTLV-1–infected $CD4^+$ T lymphocytes [5,6,7].

Hodgkin lymphoma (HL) is a monoclonal lymphoid neoplasm derived from germinal-centre B cells. Patients with Classic Hodgkin Lymphoma (CHL) usually present with painless, firm lymphadenopathy, with more than 70% of patients having palpable cervical or supraclavicular lymph nodes and more than 60% having mediastinal involvement.

The lymph node morphology of CHL is characterized by the presence of mononuclear Hodgkin cells and bi/multinucleated Reed–Sternberg cells within a non-neoplastic cellular micro-environment consisting of T cells along with variable numbers of eosinophils, histiocytes, neutrophils, plasma cells with or without the presence of epithelioid granulomas.

CASE REPORT

We report a case of 63-year-old female, who presented in October 2021 with multiple skin lesions and metabolically active lymph nodes (LN) on PET-CT scan. She was diagnosed as ATLL and was started on topical Betamethasone. Patient then referred to our instituted and undergo review of lymph node biopsies thrice from right supraclavicular LN, right inguinal LN and nasopharynx were consistent with granulomatous inflammation and hence, the patient was given anti-tubercular treatment for 18 months. Follow up PET-CT scan showed progression of disease. At the time of presentation in the hospital peripheral blood smear demonstrated absolute lymphocytosis with 85% atypical lymphoid cells (Total leucocyte count $53.23x10^9$/L). Peripheral blood immunophenotypic analysis showed 65% gated atypical lymphocytes with moderate expression of CD45, moderate CD4 and CD5, dim-moderate expression of CD38, dim-moderate cytoplasmic CD3 (cytCD3), dim CD48, CD27 positivity in subset, the population was negative for CD34, CD19, CD20, CD10, CD25, CD7, CD8, TCR gamma delta and TRBC1 markers (**Figure 1**).

The findings were consistent with CD4 positive T-cell chronic lymphoproliferative disorder. HTLV1 status was not done at the time of progression of disease.

CT-guided biopsy of mediastinal LN (**Figure 2**) cores of lymphoid tissue revealing effacement of nodal architecture by a polymorphous population of lymphoid cells consisting of atypical lymphoid cells, small mature lymphocytes, plasma cells, histiocytes and leucocytes. Few scattered Reed Sternberg-like (RS-like) cells were noted. At places, ill-defined epithelioid cell granulomas were seen. Necrosis was absent.

On immunohistochemistry, the atypical lymphoid cells were positive for CD3, CD5, CD4 and negative for CD7, CD8; while the RS-like cells were positive for CD30 and CD20 (very focal and weak), negative for PAX5 and CD15. Epstein-Barr virus-encoded RNA1 in situ hybridization (EBERISH) was negative.

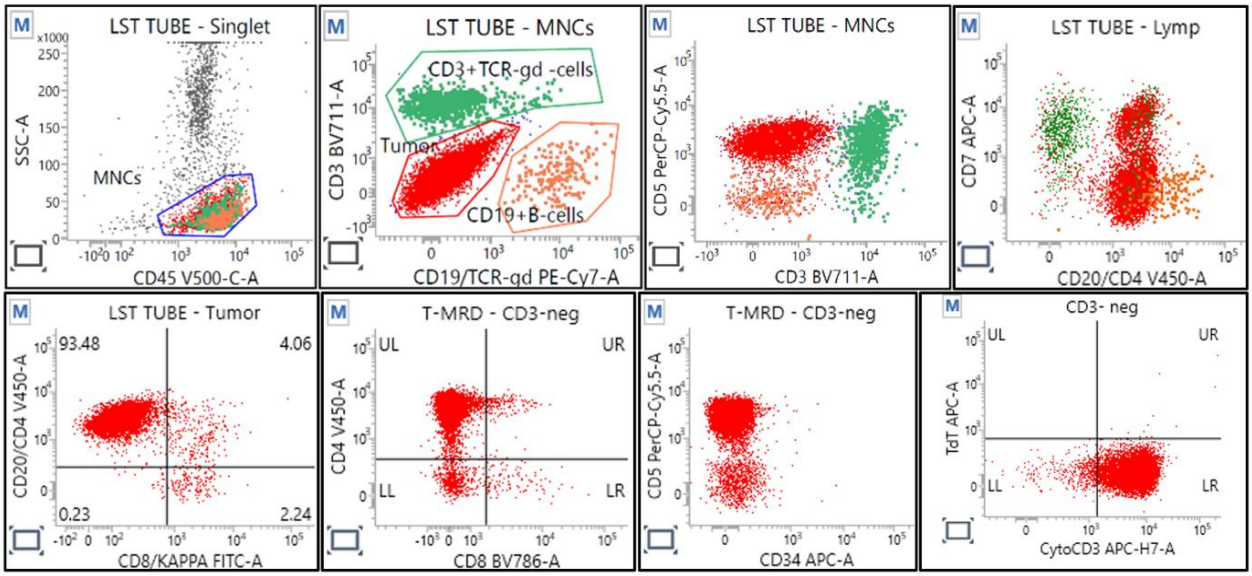

Figure 1. Immunophenotyping by flow cytometry of peripheral blood sample, illustrating 65% atypical lymphocytes expressing moderate cd45, negative cd3 and cd19, moderate cd5, moderate cd4 and negative cd8, dim-moderate cytoplasmic cd3, negative cd34. Atypical lymphoid cells (red), cd3 positive tcr gamma delta cells (green), cd19 positive b cells (orange).

Overall features were consistent with involvement of the mediastinal lymph node by T-cell non-Hodgkin lymphoma.

DISCUSSION

'Hodgkin-like' is a rare morphological variant of ATLL, which represents the incipient early neoplastic phase of ATLL with an indolent clinical course. Ohshima *et al*. examined 18 patients with Hodgkin-like ATLL and observed that approximately half of the patients developed typical ATLL within 2 or 3 years. In some of the patients, lymph nodes can show large Hodgkin-like B lymphocytes in a background of small to medium-sized ATLL cells early in the course of the disease, which may result from the underlying immunodeficiency in patients with ATLL [7,9].In such cases, lymph nodes histologically resemble Hodgkin's disease. Differential diagnosis between Hodgkin-like Adult T cell Leukemia/lymphoma and classical Hodgkin Lymphoma is challenging without performing a molecular analysis of HTLV-1. In Hodgkin-like ATLL, Reed Sternberg-like giant cells express CD30 and/or CD15 antigen, similar to RS cells in CHL; while the infiltrating lymphocytes in background, with no or minimal nuclear abnormalities exhibit a CD4-positive T-cell phenotype [7,8].

Ohshima et al concluded that the giant cells were reactive in nature and resembled immature cells of B-lineage, whereas the HTLV-I infected CD4+ T cells demonstrated clonality, which are considered to have an important role in ATLL tumorigenesis [7].

In the other study, Ohshima et al found that the local immunologic disorder or imbalance appears to influence the RS cell formation and hence, in HL-like ATLL, HTLV-1 infection might not be necessary for the formation of RS cell [8].

In ATLL cases, on immunophenotyping by immunohistochemistry and flow cytometry, the tumour cells express pan–T-cell antigens like CD2, CD3, CD5 and usually lack CD7, most of the cases are CD4 positive and CD8 negative. CD30 may be variably expressed in the larger cells. In CHL cases, the HRS cells express membranous pattern of CD30 and CD15 in majority of the cases, with accentuation in the Golgi area of the cytoplasm. The best marker for the demonstration of B-cell nature of HRS cells is PAX5, which is expressed in almost all cases.

Karube et al described 8 cases of ATLL with HTLV-1–infected HRS-like cells. They concluded that ATLL with HTLV-1–positive HRS-like cells is one of the most important differential diagnoses for lymph node lesions with CHL-like morphology in HTLV-1 carriers. CD4 positivity and PAX5 and EBER-ISH negativity are key features which point towards ATLL with HTLV-1–positive HRS-like

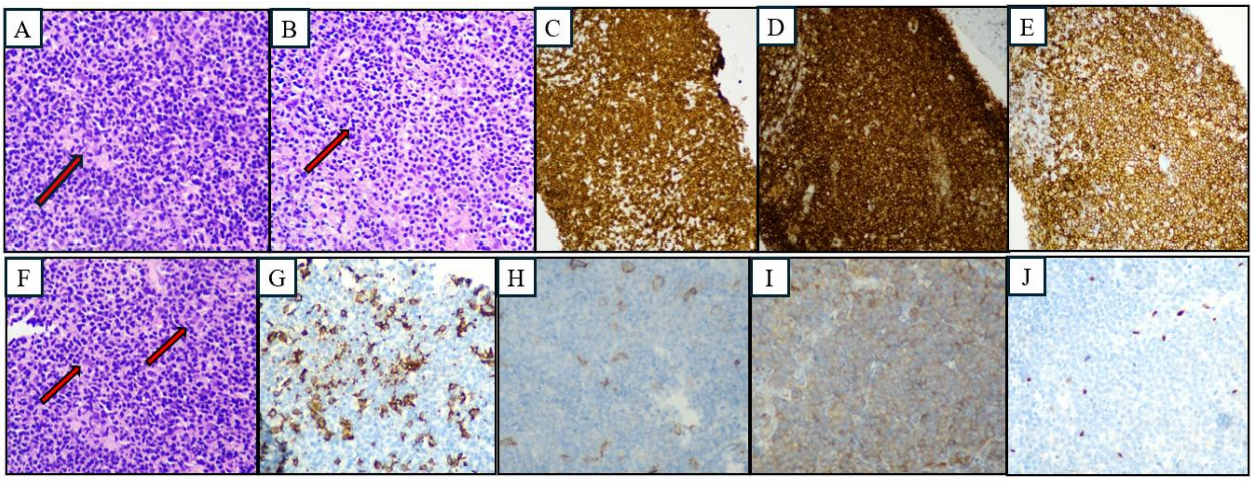

Figure 1. Granuloma H&E 40x (A); atypical lymphoid cells h&e 40x (B), positive for cd3 20x (C), positive for cd4 20x (D), positive for cd5 20x (E); reed sternberg-like cellsh&e 40x (F), positive for cd20 40x (G), positive for cd30 40x (H), negative for cd15 40x (I), negative for pax5 40x (J)

cells, and for confirming the diagnosis, diffuse positivity of ultrasensitive RNA in situ hybridization for HTLV-1 basic leucine zipper factor (HBZ-ISH) is critical. The study described that HTLV-1–infected HRS-like cells might have derived from $CD4^+$ T cells, as they often show positivity for CD4 and CD25 (the typical immunophenotype of ATLL), while the HRS cells in CHL rarely show loss of PAX5 and aberrant T-cell antigen expression. Hence, they suggested to emphasize on the phenotypic characteristics and the proportion of HTLV-1–positive cells among HRS-like cells for the distinction between HRS-like cells and HRS cells in CHL [3].

In retrospectively collected data of 1665 ATLL patients newly diagnosed from 2000 to 2009 in Japan, among acute and lymphoma subtypes, the most used multiagent chemotherapy was CHOP21 (cyclophosphamide, doxorubicin, vincristine, and prednisolone), followed by CHOP14, VCAP-AMP-VECP (a sequential combination chemotherapy consisting of vincristine, cyclophosphamide, doxorubicin, and prednisolone; doxorubicin, ranimustine, and prednisolone; and vindesine, etoposide, carboplatin, and prednisolone), ATL-G-CSF (vincristine, vindesine, doxorubicin, mitoxantrone, cyclophosphamide, etoposide, ranimustine, and prednisolone with prophylactic support by granulocyte-colony stimulating factor), and mEPOCH (etoposide, prednisolone, vincristine, carboplatin, and doxorubicin; carboplatin was substituted for cyclophosphamide). This study revealed that the prognoses of the patients with acute and lymphoma types were still unsatisfactory, despite the recent progress in treatment modalities, however the 4-year overall survival was significantly better in patients receiving ATL-G-CSF or mEPOCH[2].

Whereas Hodgkin lymphoma is considered as a highly curable disease with favorable prognosis. The frontline treatment includes polychemotherapy - either response-adapted doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) or dose-escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP), selectively combined with radiotherapy. PD-1 blockade with pembrolizumab or nivolumab is reported to be highly effective in relapsed or refractory cases [10].

The management approach and the treatment vary according to the diagnosis and subclassification of lymphomas. Hence, it is crucial to distinguish between Hodgkin lymphoma and conventional ‘Hodgkin-like’ variant of ATLL while diagnosing.

CONCLUSION

To differentiate between Hodgkin’s disease and incipient ATLL is very difficult, yet crucial, because of the difference in therapy as well as prognosis. It is important to perform the test for HTLV-1 infection in all cases of T-cell lymphoma with features of ATLL and those showing features of classic Hodgkin lymphoma where the background lymphoid cells (other than the RS-like cells) appear atypical.

A multidisciplinary approach including the correlation of peripheral blood picture with immunophenotyping along with LN biopsy and

immunohistochemistry is beneficial for the correct diagnosis of T cell lymphomas with varying degrees of morphological variations, as it is crucial for the management decisions.

Conflict of Interest

The authors declare that they have no competing interests.

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Authors' Contribution

Concept: RP, PG, NN; Design: PG, NN, RP; Data collection or processing: PG,RP,NN; Analysis or Interpretation: PP,PKS,AS,SS; Literature search: AS, NN, PKS, SS; Writing: PG,RP; Approval: AS, NN, PKS,PP, SS. All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

AI use statement

No artificial intelligence tools or generative AI were used in the creation of this work.

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