CD30 POSITIVE NON-LEUKEMIC VARIANT OF ADULT T-CELL LEUKEMIA/LYMPHOMA, HTLV-1 ASSOCIATED

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Abstract

We present a case of non-leukemic (lymphomatous) variant of HTLV-1 associated adult T-cell leukemia/lymphoma in a young woman. Tumor demonstrated strong and diffuse CD30 and PD-1 expression which is very unusual finding in this entity. Very good clinical response was obtained with brentuximab-containing treatment regimen.

CD30 POSITIVE LYMPHOMATOUS (NON-LEUKEMIC) VARIANT OF ADULT T-CELL LEUKEMIA/LYMPHOMA, HTLV-1 ASSOCIATED

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A 38-year-old previously healthy woman of Haitian origin presented with splenomegaly and extensive lymphadenopathy involving cervical, supraclavicular, axillary, mediastinal, hilar, para-esophageal, para-aortic, mesenteric and inguinal lymph nodes. The largest lymph node measured 2.9 cm in size and PET-CT scan showed maximum SUV of approximately 32 mSv. No skin lesions were identified. Serum calcium was normal. Peripheral blood counts were within normal range and no circulating abnormal lymphoid cells were seen.

The patient underwent a biopsy of a cervical lymph node. The lymph node architecture was effaced by an atypical infiltrate of large pleomorphic lymphoid cells with moderate eosinophilic cytoplasm, irregular nuclei, coarse to vesicular chromatin and occasional prominent nucleoli (Images 1 and 2) amid a background of rare small lymphocytes and histiocytes.

By immunohistochemistry, neoplastic cells were positive for CD3, CD4, CD25, and negative for CD7 (Image 3), positive for CD2, CD5, and Bcl-2 (not shown). In addition, tumor cells were strongly positive for CD30 and PD1 (Image 4), CD8, CD10, CD20, Bcl-6, ALK-1, granzyme B and CXCL-13. Neoplastic cells showed 60% Ki67 proliferation index. CD21 highlighted rare small residual follicular dendritic cell meshworks. Immunohistochemical stains for CD68 and CD138 stained admixed histiocytes and plasma cells, respectively. Flow cytometry showed an abnormal T-cell population with expression of CD4, CD2, CD5, moderate CD3, and lack of CD7. Serologic tests showed anti-human T-cell leukemia virus (HTLV)-1/2 antibodies with subsequent Western blot confirmation of HTLV-1 infection. In this context, the histopathologic

and immunophenotypic findings were consistent with adult T-cell leukemia/lymphoma (ATLL), HTLV-1 associated.

Staging bone marrow evaluation did not demonstrate involvement by lymphoma. Evaluation of cerebrospinal fluid showed no abnormal cells by cytology or flow cytometry. The patient began treatment with brentuximab, cyclophosphamide, adriamycin, vincristine, etoposide and prednisone (BvCHEP) with intrathecal methotrexate with significant improvement in adenopathy after one cycle. Treatment is planned for a total of four cycles followed by allogenic stem cell transplant.

HTLV-1 retrovirus has been present since ancient times [1]. Its prevalence is very low (<0.1%) in the general population but exceeds 1% in certain areas of Caribbean, Pacific and Africa [2]. HTLV-1 has a particularly high tropism for CD4 lymphocytes. Via binding of HTLV-1 envelope surface proteins to CD4 surface receptors and subsequent fusion with a target cell, viral RNA is delivered into the cytoplasm, converted by reverse transcriptase into double-stranded DNA which, in turn, is shuttled into the nucleus and is incorporated into the T-cell genome as provirus, which can be detected by quantitative PCR in peripheral blood mononuclear cells [3].

The major difference between HIV and HTLV-1 is the fact that the latter stimulates mitosis of target CD4 T-cells rather than viral replication [2]. That is why, in contrast to HIV infection, patients with HTLV-1 infection have normal or high, rather than low, CD4 counts. In addition, viral transmission between persons occurs through infected cell transfer and not by cell-free virus. Major mechanisms of infectivity are breast-feeding, blood transfusion and sexual transmission [3]. It has been estimated that in HTLV1-endemic areas, 15-25% of children of infected mothers are also infected by the virus [4]. Major diagnostic essays of HTLV-1 infection include initial serum enzyme-linked immunosorbent assay-based screening test, with subsequent confirmation by Western blot.

All HTLV-1 related disorders are broadly classified into neoplastic, inflammatory and infectious. Neoplastic HTLV-1 associated disorder is represented by ATLL, and examples of infectious and inflammatory HTLV-1 related entities include, but are not limited to, tropical spastic paraparesis (also known as HTLV-1 associated myelopathy), dermatitis, arthritis, uveitis and myositis.

The 2017 WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues separates four clinical variants of ATLL: smoldering, chronic, acute and lymphomatous [5,6]. Recently, extranodal primary cutaneous variant of ATLL has been described [5]. In contrast to most described cases of ATLL, our patient presented with isolated lymphadenopathy, without involvement of peripheral blood, bone marrow or skin. Therefore, it is best classified as the lymphomatous type of ATLL.

Strong and diffuse expression of CD30, as seen in our case, is an unusual finding in ATLL. However, Takeshita et al described expression of CD30 in 21 of 91 Japanese patients with ATLL [7]. Like our case, patients in their study presented with lymphomatous variant of ATLL, with only rare cases showing leukemic disease. As a non-specific activation marker, CD30 may be expressed by a number of non-Hodgkin lymphoma (NHL) subtypes including ATLL, which should be considered in the differential diagnosis of CD30-positive lymphoproliferative disorders. Moreover, the availability of brentuximab vedotin, a targeted anti-CD30 monoclonal antibody-based therapy, mandates assessment of CD30 expression in T-cell NHL. Also observed in our case was PD-1 expression by tumor cells, a feature that may provide a rationale for immune checkpoint inhibitor treatment, which to date has shown variable results in phase 2 trials of ATLL [8,9].

Key clinical message : Non-leukemic variant of HTLV-1 associated adult T-cell leukemia lymphoma (ATLL) is a rare variant, and herein we describe a case with strong and diffuse positivity of neoplastic cells for CD30. Even though ATLL is aggressive entity with poor prognosis, in our case, there was very good clinical response achieved with Brentuximab-containing regimen. Therefore, HTLV-1 associated ATLL can be included in the differential diagnostic approach of CD30-positive lymphoproliferative disorders.

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