Case Report: Orbital Tumor Revealing Adult T-Cell Leukemia/Lymphoma Associated with Human T-Cell Lymphotropic Virus Type-1

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Abstract. Adult T-cell Leukemia/Lymphoma (ATLL) is a sight- and life-threatening complication of human T-cell lymphotropic virus type 1 (HTLV-1) infection. Ophthalmic manifestations include uveitis, optic nerve oedema, retinal vasculitis, and lymphomatous infiltration. Orbital lesions are rare. We report the case of an orbital tumor revealing systemic ATLL in a 45-year-old Dominican patient who died despite treatment. Apart from late-grade cutaneous T-cell lymphoma, ATLL is the only T-lymphoma to develop in the orbit. Diagnosis is based on serologic evidence of HTLV-1 infection, cytology, and blood sample analysis. Biopsy is deemed necessary. Given the poor prognosis of ATLL and the worldwide presentation of HTLV-1, physicians should consider ATLL in the differential diagnosis of orbital malignant tumor and look for HTLV-1 infection in populations at risk.

INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV-1) is the first discovered retrovirus associated with human diseases. About 10 to 20 million people are infected with HTLV-1 throughout the world.¹ The infection is endemic to the Caribbean Islands, South and Central America, Africa and southern Japan.² It can be transmitted from mother to child, through sexual contact, and through contact with contaminated blood. Common ocular presentations of HTLV-1 are uveitis, keratoconjunctivitis sicca, and interstitial keratitis.^{3–5} The vast majority of infected people are asymptomatic for life. However, HTLV-1 can induce severe systemic diseases, such as HTLV-1 associated myelopathy/tropical spastic paraparesis and adult T-cell leukemia/lymphoma (ATLL).^{6,7} ATLL is a mature T-cell non-Hodgkin lymphoma with a leukemic phase and is characterized by the circulation of activated CD4+ T-cells. The incidence rate of ATLL is 61 per 100,000 HTLV-1 carriers.⁸ Diagnostic criteria for ATLL include seropositivity for HTLV-1 and circulating atypical lymphocytes (“flower cells”) with T-cell markers.⁹ ATLL clinical presentation is the same as many other lymphomas and can include adenomegaly, hepatosplenomegaly, skin lesions, and hypercalcemia. T-cell lymphomas rarely invade the orbits. We report the case of a Dominican patient with an orbital mass and infiltration of ethmoid, frontal, and maxillary sinuses secondary to ATLL.

CASE REPORT

A 45-year-old Dominican man with no significant medical history was presented to the University Hospital of Martinique in April 2016 for transient loss of consciousness. Physical examination revealed bilateral cervical adenomegaly and left exophthalmos, which prompted ophthalmic examination (Figure 1). The patient was drowsy. He reported pain behind the left eye, lagophthalmos for 2 weeks and binocular diplopia, but no decreased vision. He had no history of blood transfusion. He had no known allergies and no ongoing treatment.

He had a family history of ATLL in his mother. Visual acuity was 20/25 OU. The pupils were equal and symmetric and there was no relative afferent pupillary defect. Ocular movements were full, with the exception of upgaze limitation in the left eye. Slit-lamp examination showed deep and quiet anterior chambers. Dilated fundus examination was unremarkable. More specifically, there were no vitreous cells or flare. Fluorescein angiography showed normal retinal perfusion and no intraretinal proliferation. White blood cells count was 12.3 G/L (normal range, nr: 4–10 G/L), including 2.95 G/L lymphocytes (nr: 1–4 G/L) with a majority (2.58 G/L) of irregular polylobated flower-like nuclei. Immunological phenotype was helper T-cell, consistent with lymphoproliferative syndrome. HTLV-1 antigens were detected in blood cells and confirmed by western blot. Proviral load was of 834,277 copies per million cells in blood sample using real-time polymerase chain reaction assay. It was of 1,266,443 copies per million cells in cerebrospinal fluid. Anti-Tax antibodies were not tested. Serum calcium was of 4.72 mM (nr: 2.15–2.55 mM) and lactate dehydrogenase (LDH) was 2,700 U/L (nr: 135–225 U/L). Head, chest, and abdomen CT-scan with contrast revealed a large mass in the left eye socket, causing grade III exophthalmos. The mass extended

FIGURE 1. Left exophthalmos with extra-axial downward displacement of the globe. Pupils are pharmacologically dilated. This figure appears in color at www.ajtmh.org.

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TABLE 1
Summary of previous case reports of adult T-cell leukemia/lymphoma orbital tumors

Article first author, year of publication	Age (year), gender	Ethnicity	Initial presentation of ATLL	Delay between ATLL diagnosis and orbital location	Treatment of orbital location	Outcome
Lauer et al., 1988 ¹⁵	41, M	Jamaican	Skin rash on the back chest and face	3 y	Local radiation therapy	Died 3 months after orbital location
Mori et al., 2003 ¹⁶	43, F	Japanese	Right cervical lymphadenopathy and left ventricle tumor	10 y	Etoposide vindesine carboplatin	Not reported
Yoshikawa et al., 2005 ¹⁷	64, M	Japanese	Bilateral orbital tumor	0	Vincristine, doxorubicin, cyclophosphamide, prednisolone	No recurrence over a year after chemotherapy
Esmaeli et al., 2001 ¹⁸	40, F	Not reported	Not reported	1 y	Chemotherapy allogenic bone marrow transplantation	No recurrence of disease 3 months after treatment

ATLL = adult T-cell leukemia/lymphoma; F = female; M = male; y = year.

into the maxillary, ethmoid and frontal sinuses, and into left frontal lobe but without mass effect (Figure 2). There were bilateral cervical, mediastinal, and supraclavicular adenomegalies without bone destruction or pulmonary lesion. Biopsies of the orbital mass and left ethmoid sinus confirmed the diagnosis of ATLL (Figure 3).

The patient received chemotherapy that consisted of Interferon- α with zidovudine. His clinical course was complicated by recurrent episodes of chemotherapy-induced neutropenia. In June 2016, he complained of decreased bilateral vision without pain or redness. Dilated fundus examination revealed vitreous and preretinal hemorrhages consistent with Terson's syndrome (Figure 4). The patient died in July 2016, 4 months after the diagnosis of ATLL.

DISCUSSION

Ophthalmic manifestations in ATLL include uveitis, optic nerve edema or thickening, retinal vasculitis with lymphomatous infiltration, and retinal necrosis linked to cytomegalovirus infection.^{10–14} In the setting of ATLL, orbital lesions are rare. To our knowledge, only four cases of ATLL-related orbital tumors have been reported (Table 1).^{15–18} However, lymphoid neoplasms represent 10% of orbital tumors and are the most common primary orbital tumor among adults over 60.¹⁹ Most

orbital lymphoma are extranodal marginal-zone B-cell lymphomas of mucosa-associated lymphoid tissue type (MALT).²⁰ Few T-cell lymphomas can develop in the orbits. They include mycosis fungoides and Sezary syndrome, which share some clinical and histopathological similarities with ATLL. In the case of ATLL, the orbital location might be related to HTLV-1 neurotropism. Indeed, HTLV-1 antibodies were found in the cerebrospinal fluid of patients with HAM/TSP.⁶ It is possible that HTLV-1 infects neurological cells in the orbit, promoting the development of ATLL cells years or decades later. In our case, the patient's mother was treated for ATLL but we had no information concerning the duration of her infection. We hypothesize that there was a mother-to-child transmission at birth or by breastfeeding, resulting in infection 45 years before the onset of ATLL. This would indicate that ATLL development may be correlated with T-cell infection early in life, as some studies have demonstrated.^{21,22} Another hypothesis would involve "family aggregation." Relatives of people with ATLL could be at a higher risk of developing ATLL owing to shared genetic factors.²³

Orbital tumor as the onset of ATLL is exceptional. The only case was reported by Yoshikawa et al.¹⁷ They described the occurrence of bilateral orbital tumor causing exophthalmos and eyelid edema but no systemic symptoms in a 64-year-old Japanese man. Biopsies confirmed the diagnosis of ATLL.

FIGURE 2. Head CT-scan with contrast: Large orbital mass with left grade III exophthalmos, invasion of the ethmoid sinus (A) and the left frontal lobe (B). There is necrosis of the orbital plate frontal bone (C).

FIGURE 3. Orbital mass pathology. (A) Hematoxylin-eosin, original magnification $\times 7$. Diffuse infiltration of atypical lymphocytes. Multiple mitotic pleomorphic leukocytes (black arrow). (B) The lymphocytes were positive for CD3 (red arrow) and CD4 and negative for CD7 and CD56. (C) Ki-67 marker (yellow arrow) was positive in more than 90% of atypical lymphoid cells, showing high degree of proliferation and malignancy (bad prognosis factor).

The patient was treated with vincristine, doxorubicin, cyclophosphamide, and prednisolone—with good results. Our patient's health deteriorated very quickly after presentation although he presented no systemic symptoms before the ocular manifestation. He died of Aspergillus pneumonia 4 months after being diagnosed with ATLL. Among the previous reports of orbital involvement in ATLL, only one patient out of four died within the first 3 months following diagnosis.¹⁵ Starting treatment as soon as possible is, therefore, critical for the prognosis, especially in patients with ocular involvement at onset.²⁴ Biopsies are no longer necessary for the administration of chemotherapy in patients fulfilling the following criteria for ATLL: positive HTLV-1 serology, abnormal lymphoid cells with multi-lobulated nuclei and ATL-type T-cell markers, hypercalcemia, lymphadenopathy, and either hepatosplenomegaly or skins lesions.⁹

Despite a variety of new therapeutic approaches tested over the last 30 years, the prognosis of ATL remains poor. Allogenic hematopoietic stem cell transplantation remains one of the best curative therapies.²⁵ A novel approach, however, includes daclizumab, a monoclonal antibody, directed against IL-2 receptor.²⁶

Median survival time oscillates between 6 months and a year.²⁷ Some biological factors have been associated with poor prognosis, such as $\beta 2$ -microglobuline, interleukin-2 receptor, hypercalcemia, high expression of the Ki67 antigen, and high levels of lactate dehydrogenase.²⁸ The last three were observed in our patient. He was treated with a combination of interferon-alpha and zidovudine, which commonly achieve a good remission rate with moderate toxicity.

FIGURE 4. Right eye (A) and left eye (B) fundus photographs showing bilateral preretinal and intravitreal hemorrhages in the setting of Terson syndrome.

Given the poor prognosis of ATLL and the fact that HTLV-1 is present throughout the world, with clusters of high endemicity, physicians should consider ATLL in the differential diagnosis of orbital malignant tumor and look for HTLV-1 infection in populations at risk. Physicians should be aware that biopsy is not always necessary for diagnosis if there is a cluster of arguments for ATLL. Such cluster, if present, allows the beginning of chemotherapy as soon as possible.

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