EXCEPTIONAL CASE REPORT

blood global hematology

Primary central nervous system adult T-cell leukemia/lymphoma: diagnostic challenges

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Key Points

- We describe a case of isolated CNS involvement of ATLL, a preventable T-cell neoplasm.
- Advances in flow cytometry, particularly in clonality assessment, can aid the diagnosis of similar cases.

Adult T-cell leukemia/lymphoma (ATLL) is a rare lymphoid neoplasm associated with human T-cell lymphotropic virus type 1 (HTLV-1). The disease has a heterogeneous presentation, and central nervous system (CNS) involvement occurs in 5% to 20% of cases, usually with concomitant systemic disease. We present a case of a female aged 45 years, previously known to be a HTLV-1 carrier, who developed neurological symptoms and was finally diagnosed with primary CNS ATLL after imaging studies and flow cytometry analysis of cerebrospinal fluid showed a proliferation of clonal T cells.

Introduction

Adult T-cell leukemia/lymphoma (ATLL) is a rare lymphoid neoplasm, with an estimated incidence of 0.05 cases per 100 000 people.[1] As a human T-cell lymphotropic virus type 1 (HTLV-1) associated disease, its incidence mirrors the prevalence of the infection with this retrovirus, which is endemic in Asia (particularly in Japan), the Caribbean Islands, Africa, and South America. The transmission occurs vertically (through breastfeeding or in utero), by sexual intercourse, blood transfusion, or contaminated solid organ transplant. Most carriers of HTLV-1 are asymptomatic and will not experience any consequences of the infection throughout life. However, a small fraction (3%-5%) will develop ATLL, with a median age at diagnosis of between 60 and 70 years. The disease presentation is polymorphic, ranging from smoldering, a stage with mild disease burden and skin manifestations, to the acute presentation, with lymphocytosis, lymphadenopathy, and marked hypercalcemia.[2,3] To encompass the diversity of ATLL clinical presentation, a classification was described in 1991 by Shimoyama and readily adopted as a standard in the field.[4,5]

Central nervous system (CNS) disease affects 5% to 20% of patients with aggressive (acute or lymphomatous) ATLL at diagnosis and is even more frequent during relapses.[6,7] This led to the recommendation from an expert panel to perform diagnostic lumbar puncture and prophylaxis with intrathecal chemotherapy or systemic agents that cross the blood-brain barrier in order to diagnose and prevent CNS disease, respectively.[8] In fact, the addition of these drugs to treatment protocols seems to have impacted the CNS relapse rate.[9]

Submitted 26 March 2026; accepted 20 May 2026; prepublished online 4 June 2026. https://doi.org/10.1016/j.bglo.2026.100111.

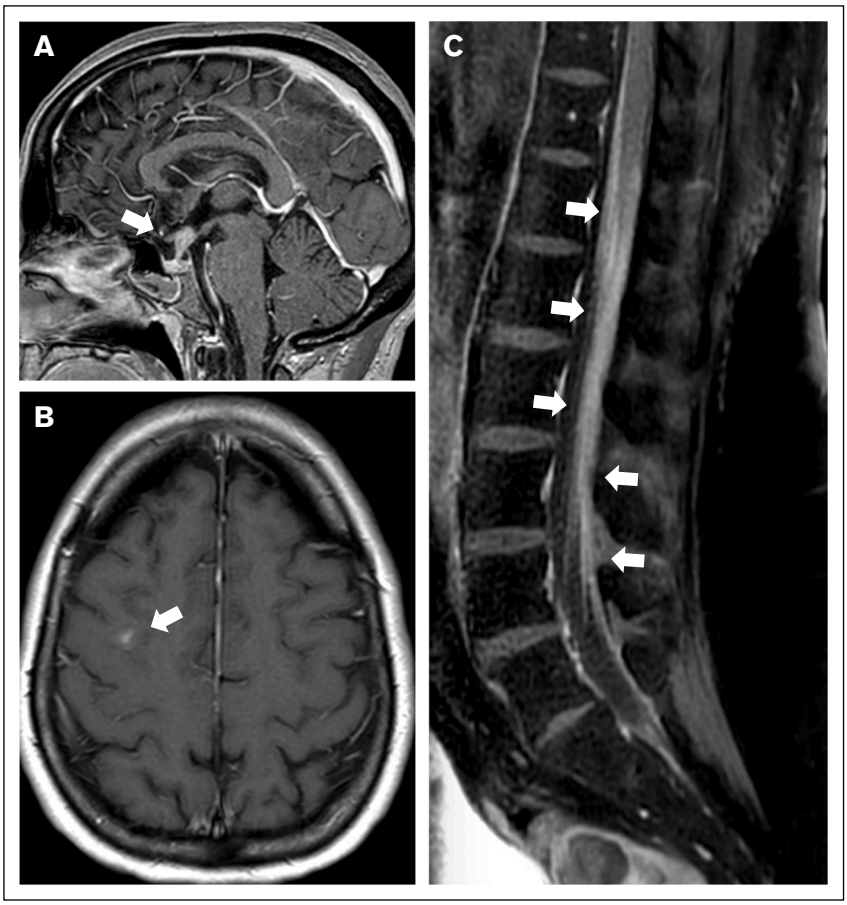

Figure 1. Magnetic resonance imaging diagnostic images from the presented case. (A) Sagittal T1-weighted brain scan with thickening and intense enhancement in the anterior aspect of the hypothalamus, involving the infundibular recess and the infundibulum. (B) Axial T1-weighted brain scan with a right frontal lesion with intense contrast enhancement. (C) Sagittal T1-weighted spine scan showing thickening and marked contrast enhancement of cauda equina roots.

Although CNS disease is not an infrequent phenomenon in ATLL, the presentation of isolated CNS disease is an uncommon finding and poses diagnostic and therapeutic challenges.

Case description

A female aged 45 years was admitted to the emergency service because of hypoesthesia and paresis of both legs, especially in the proximal musculature. In the previous month, she had complained of lower back pain with irradiation in both legs but did not seek medical attention. Her medical history was unremarkable, except for systemic arterial hypertension and a diagnosis of HTLV-1 carrier status uncovered after a blood donation. Blood counts at admission were as follows: hemoglobin 12.4 g/dL, white blood cells 8860 per mm^3 (neutrophils 7620 per mm^3, lymphocytes 9%, monocytes 3%, and eosinophils 2%), platelets 294 × $10^3/\mu L$. Biochemistry studies showed slightly elevated lactic dehydrogenase (243 U/L; normal, <234 U/L) and marginally low ionic calcium (4.3 mg/dL; normal, 4.6-5.16 mg/dL), whereas kidney function and hepatic parameters had no significant alterations. Because of the neurological symptoms, brain and lumbar magnetic resonance imaging were performed and showed thickening and impregnation by paramagnetic contrast in the anterior aspect of the hypothalamus, in the trigeminal nerves, and, additionally, a small lesion in the cortico-subcortical region in the right frontal convexity. In the spine, intense contrast uptake was observed in the conus medullaris and roots of the cauda equina (Figure 1).

Lumbar puncture with cerebrospinal fluid (CSF) analysis showed the following: glucose 35 mg/dL, total protein 618 mg/dL, 1110 nucleated cells per mm^3 composed by 100% of mononuclear cells. Morphologically, the cells resemble mature lymphocytes, some with jagged chromatin. Flow cytometry analysis of the CSF confirmed a T-cell lymphocyte clonal proliferation positive for CD45, CD3, CD2, CD4, CD5, CD38 and negative for CD7, CD8, CD56, and TCRB1 (Figure 2). Peripheral blood was then assessed, and neither flower cells nor clonal lymphocytes were detected by morphology or flow cytometry, respectively. Computerized tomography of the neck, thorax, and abdomen showed neither lymph node enlargement nor hepatosplenomegaly. So, the lymphoproliferative disease was deemed to affect only the CNS. In the context of an HTLV-1 carrier, with positive serology and confirmatory polymerase chain reaction, a diagnosis of primary CNS ATLL was made.

During the hospital stay and before the start of treatment, new neurological symptoms appeared: eyelid ptosis, diplopia, and visual hallucinations. Treatment was started with oral zidovudine 300 mg every 8 hours concurrently with high-dose antimetabolites, consisting of methotrexate 3500 mg/m^2 IV on the first day and cytarabine 2000 mg/m^2 IV every 12 hours on days 2 and 3 (total of 4 doses per cycle). Triple intrathecal chemotherapy was also associated. CSF examinations showed a progressive clearance of neoplastic cells, with 5 nucleated cells per millimeter square after 2 cycles. Magnetic resonance imaging lesions, however, were

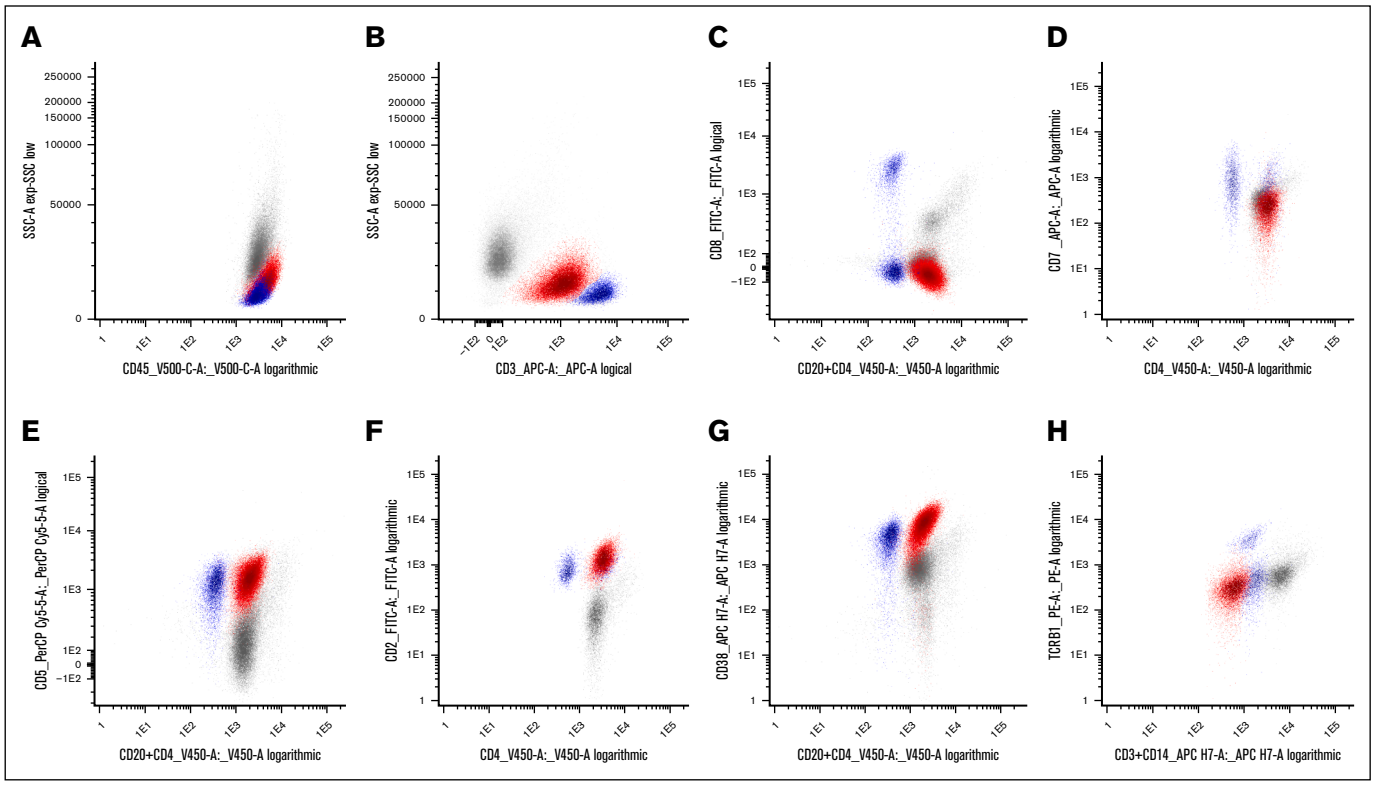

Figure 2. Flow cytometry dot plots from CSF. Red: anomalous clonal T-lymphocyte population; blue: normal lymphocyte population; gray: primarily monocyte population. Side scatter (SSC-A) vs CD45 (A) shows the initial gating strategy, distinguishing lymphocytes (low SSC-A, high CD45, represented by red and blue populations) from monocytes (intermediate SSC-A and intermediate CD45, represented by the gray population). The anomalous clonal T-lymphocyte population has lower CD3 positivity than the normal one (B), is $CD4^{+}CD8^{-}$ (C), and lacks CD7 expression (D). The anomalous population is additionally $CD5^{+}$ (E), $CD2^{+}$ (F), and has high CD38 expression (G). (H) The complete absence of TRBC1 expression in the anomalous T-lymphocyte population indicates a clonal T-cell expansion that is $TRBC2^{+}$.

almost unchanged. Despite the use of prophylactic granulocyte colony-stimulating factor, she developed febrile neutropenia and died from a multidrug-resistant bacteria bloodstream infection nearly 3 months after admission.

The project of this case report has been approved by the institutional ethics committee (project number: 86062724.4.0000.5121), and the application of an informed consent form was waived as the patient is dead.

Results and discussion

ATLL accounts for ≤17% of mature T-cell lymphoproliferative disorders in Latin America and, as an HTLV-1–associated neoplasm, it disproportionately affects low- and middle-income countries.[10] Effective treatments for ATLL remain an unmet medical need, particularly in the face of the recent shortage of interferon alfa-2a. CNS involvement remains especially challenging because of the laborious diagnostic process and the necessity of using drugs able to cross the blood-brain barrier.

We report a case of ATLL with atypical presentation, as the disease was restricted to the CNS. To our knowledge, only 3 cases of ATLL with isolated CNS involvement at initial presentation have previously been reported. Marshall et al reported a case of a man aged 42 years with an extensive CNS involvement by ATLL associated with herpes encephalitis.[11] He received doxorubicin, cyclophosphamide, and steroids as therapy and died <4 months after diagnosis. Autopsy confirmed that the disease was restricted to the CNS. Dungerwalla et al wrote about a man aged 38 years who presented with frontal and parietal masses and no evidence of systemic disease.[12] Treated with the modified MACOP chemotherapy protocol (doxorubicin, cyclophosphamide, methotrexate, vincristine and prednisolone) and whole brain radiotherapy, he achieved only a transient response. A second and more durable response was obtained with zidovudine plus interferon, but he ultimately progressed with systemic disease. The third case, reported by Ma et al, was about a woman aged 50 years initially with CNS-restricted manifestations that also progressed to systemic symptoms 2.5 years after initial presentation.[13] Additionally, Nishiyama et al previously described a case of ATLL relapse confined to the CNS.[14]

Some similarities between the cases must also be highlighted: the overall poor prognosis and the apparent high rate of associated infections, the latter being a recognized feature in ATLL. However, our case differs from the others by the marked meningeal involvement that allowed a diagnosis based on CSF analysis. CNS involvement by ATLL has long been described to preferentially involve leptomeninges, and recent advances in flow cytometry techniques, including clonality assessment by TCRB1, allowed us to easily establish the diagnosis. Advances in methods like this have the potential to unveil cases of CNS-isolated ATLL that go underdiagnosed, particularly in low- and middle-income countries.

It is important to note that the presented case, along with the previously reported cases, did not fit well into the current ATLL classification. More data are needed about the natural story, prognosis, and genetic features of cases presenting with isolated CNS disease to evaluate whether they represent a distinct group within the ATLL spectrum, deserving the creation of a primary CNS variant of the lymphoma type.

Authorship

Contribution: L.P.d.A. and F.L.N. reviewed the case and wrote the manuscript; P.B.A.d.S.D. reviewed magnetic resonance imaging and selected those for publication; and D.M.V.A. and N.N.N.M. performed the original cerebral fluid analysis and produced the flow cytometry plots.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

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References

1. Mehta-Shah N, Ratner L, Horwitz SM. Adult T-cell leukemia/lymphoma. *J Oncol Pract*. 2017;13(8):487-492.
2. Dittus C, Sloan JM. Adult T-cell leukemia/lymphoma: a problem abroad and at home. *Hematol Oncol Clin North Am*. 2017;31(2):255-272.
3. Bangham CRM. HTLV-1 persistence and the oncogenesis of adult T-cell leukemia/lymphoma. *Blood*. 2023;141(19):2299-2306.
4. Shimoyama M. Diagnostic criteria and classification of clinical subtypes of adult T-cell leukaemia-lymphoma: a report from the Lymphoma Study Group (1984-87). *Br J Haematol*. 1991;79(3):428-437.
5. World Health Organisation. *Haematolymphoid Tumours*. 5th ed. World Health Organisation; 2024.
6. Zing N, Fischer T, Federico M, Chiattone C, Ferreri AJM. Diagnosis, prevention and treatment of central nervous system involvement in peripheral t-cell lymphomas. *Crit Rev Oncol Hematol*. 2021;167:103496.
7. Zing NPC, Fischer T, Miranda E, et al. Central nervous system involvement in aggressive ATLL: can we predict the risk in a devastating complication? Epidemiology and clinical features from Latin America. A collaborative study from Grupo De Estudio Latino-Americano De Linfoproliferativo (GELL). *Blood*. 2024;144(suppl 1):3064.
8. Cook LB, Fuji S, Hermine O, et al. Revised adult T-cell leukemia-lymphoma international consensus meeting report. *J Clin Oncol*. 2019;37(8):677-687.
9. Tsukasaki K, Utsunomiya A, Fukuda H, et al; Japan Clinical Oncology Group Study JCOG9801. VCAP-AMP-VECP compared with biweekly CHOP for adult T-cell leukemia-lymphoma: Japan Clinical Oncology Group study JCOG9801. *J Clin Oncol*. 2007;25(34):5458-5464.
10. Valcarcel B, Idrobo H, Pavlovsky A, et al. Prevalence and survival outcomes of adult T-cell leukemia/lymphoma in Latin America: a multicenter cohort study and recommendations to improve diagnosis and outcomes. *Cancer Epidemiol*. 2025;98:102890.
11. Marshall AG, Pawson R, Thom M, Schulz TF, Scaravilli F, Rudge P. HTLV-I associated primary CNS T-cell lymphoma. *J Neurol Sci*. 1998;158(2):226-231.
12. Dungerwalla M, Osuji N, Waldman AD, et al. Isolated central nervous system involvement in adult T-cell lymphoma/leukaemia. *Br J Haematol*. 2005;130(4):511-515.
13. Ma W-L, Li C-C, Yu S-C, Tien H-F. Adult T-cell lymphoma/leukemia presenting as isolated central nervous system T-cell lymphoma. *Case Rep Hematol*. 2014;2014:917369.
14. Nishiyama T, Johkura K, Johmura Y, Momoo T, Yamada H, Kuroiwa Y. Encephalitis with MRI abnormality as a manifestation of central nervous system involvement of adult T cell leukemia/lymphoma. *Eur Neurol*. 2001;46(4):218-220.