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CASE REPORT

Aleukemic T-lymphoblastic leukemia/lymphoma with massive cerebrospinal fluid infiltration

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Abstract

T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) is an aggressive lymphoid malignancy, frequently involving the central nervous system (CNS). However, exclusive CNS infiltration of T-ALL without leukemic presentation at initial diagnosis is extremely rare. Herein, we report the case of a 19-year-old male patient who presented with progressively worsening head and neck pain, dysphagia, and dizziness. No leukemic cells were detected in peripheral blood or bone marrow samples. Computed tomography revealed only a small anterior mediastinal mass and mildly high density in some areas of the bone marrow. Although brain magnetic resonance imaging (MRI) showed no abnormal findings, spine MRI revealed slight contrast enhancement of the cauda equina. A spinal tap revealed massive infiltration of abnormal lymphoid cells that were diagnosed as T-ALL/LBL based on morphological and immunophenotypic findings. Urgent intravenous and intrathecal chemotherapeutic intervention resulted in a rapid reduction in leukemic cells in the cerebrospinal fluid, with relief of symptoms. Since T-ALL/LBL usually exhibits leukocytosis associated with a high frequency of CNS involvement, this case is considered an exceptional presentation. Recognition of such a rare presentation of T-ALL/LBL, which mimics other neurological diseases such as meningoencephalitis and demyelinating diseases, is important to avoid delayed diagnosis and treatment that could result in early death or severe neurological sequelae.

Keywords T-lymphoblastic leukemia/lymphoma · Central nervous system infiltration · Aleukemic leukemia · Intrathecal chemotherapy · High-dose methotrexate

Introduction

T-lymphoblastic leukemia/lymphoma (T-ALL/LBL) is an aggressive hematological neoplasm of precursorT-cell lymphoblasts that typically exhibits elevated leukocyte count and often accompanied by a large mediastinal mass or tumor at another site [1]. Various extranodal lesions can also develop, and central nervous system (CNS) involvement at initial diagnosis is common in T-ALL [1], which is associated with poorer prognosis than that in cases without CNS involvement [2]. Increased peripheral blood leukocyte count could be associated with CNS involvement [3]. However, massive CNS infiltration of T-ALL/LBL without leukemic presentation at initial diagnosis has rarely been reported in the literature.

Case report

A 19-year-old male patient without any remarkable medical history experienced headache, neck pain, nausea, dysphagia, dizziness, and difficulty in walking that progressively worsened over a month. Although the patient was initially admitted to the neurology department due to suspicion of demyelinating disease, he was referred to our department of hematology due to detecting large abnormal cells in the CSF, which raised doubts about hematologic malignancy. At his presentation to our department, the patient was afebrile and alert. However, he was unable to move due to severe

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head and neck pain. Mild dysarthria and dysphagia were observed, whereas other neurological deficits were absent. Complete blood count showed only slight neutrophilia and polycythemia (white blood cell count 9800/μL, with 82% neutrophils, 12% lymphocytes, 6% monocytes, without abnormal cells; hemoglobin, 17.1 g/dL; platelets, 354×10^3/μL). No coagulation disturbances were observed. Serum biochemical analysis revealed slightly elevated lactate dehydrogenase (LDH) levels (237 U/L). C-reactive protein and soluble interleukin-2 levels were not elevated (0.08 mg/dL and 274 U/mL, respectively). Although computed tomography (CT) revealed a small anterior mediastinal mass and mildly increased density in some areas of the bone marrow, no other abnormalities such as lymphadenopathy or hepatosplenomegaly were seen. Brain magnetic resonance imaging (MRI) showed no abnormal findings. However, spinal MRI revealed slight contrast enhancement of the cauda equina.

Bone marrow aspiration and biopsy revealed no abnormal cells, which was confirmed by flow cytometry (FCM) and immunohistochemical analysis. We performed repeat spinal tap, which revealed massive infiltration of abnormal lymphoid cells (2192 cells/μL) and elevated levels of LDH and sIL-2R (115 U/L and 533 U/mL, respectively) in the CSF. FCM analysis showed that the abnormal cells were CD45^{dim+}, CD1a^{-}, CD2^{+}, cytoplasmic CD3^{+}, surface CD3^{-}, CD4^{-}, CD5^{dim+}, CD7^{+}, CD8^{dim+}, CD10^{+}, CD13^{+}, CD19^{-}, CD20^{-}, CD30^{-}, CD34^{-}, CD56^{-}, and HLA-DR^{-} (Fig. 1a). Terminal deoxynucleotidyl transferase (TdT) level was insignificant. Moreover, neither immunoglobulin light chains nor T-cell receptors were expressed (Fig. 1a). Residual normal T-cell population with CD45$^{bright+}$, surface CD3^{+}, and TCRαβ^{+} phenotype were also detected. May-Giemsa staining of the CSF revealed medium-sized abnormal cells with delicate chromatin, distorted nuclei,

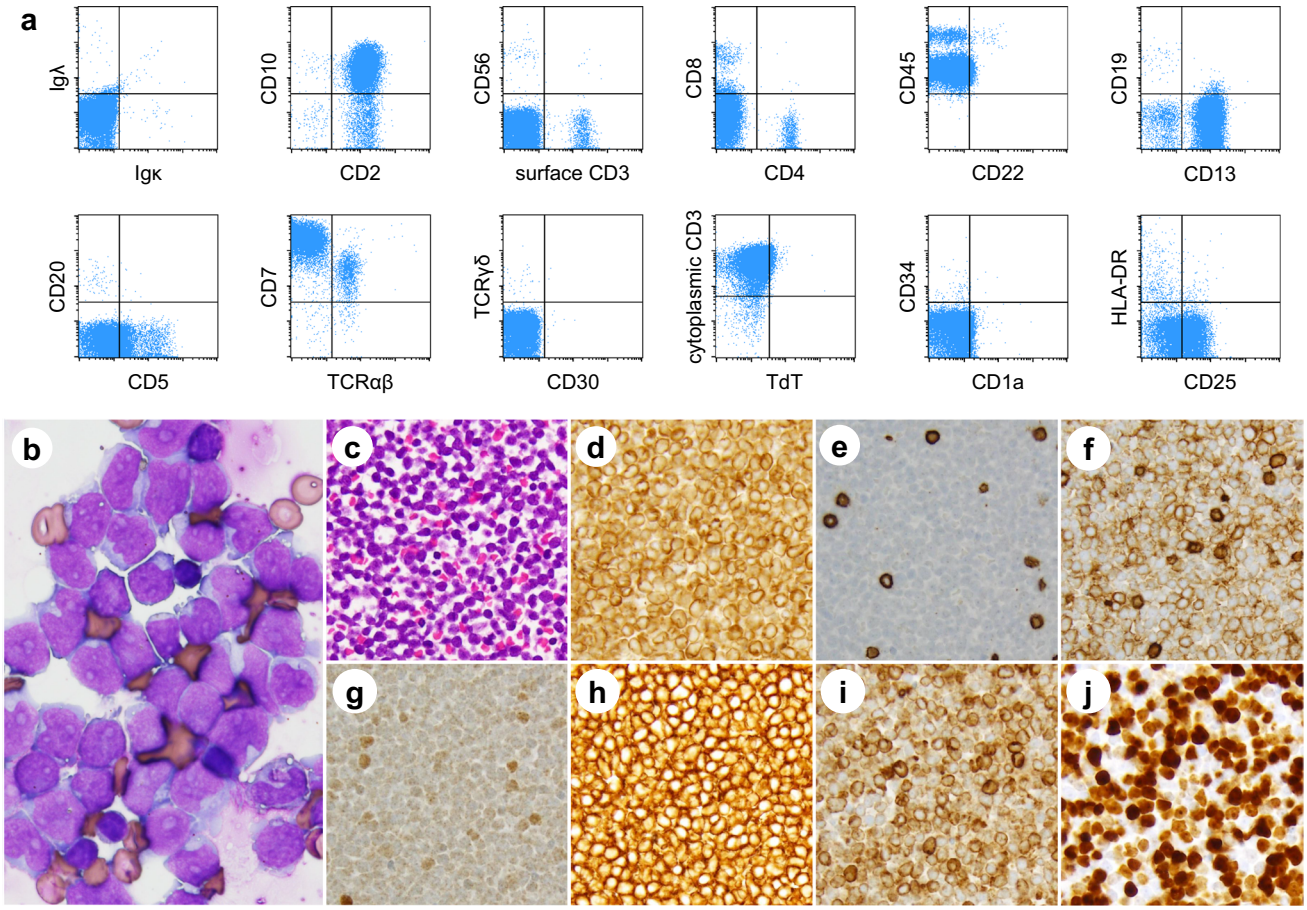

Fig. 1 Findings of leukemic cells in CSF. **a** Flow cytometry analysis shows that the abnormal cells are CD45^{dim+}, CD2^{+}, cytoplasmic CD3^{+}, surface CD3^{-}, CD4^{-}, CD5^{dim+}, CD7^{+}, CD8^{dim+}, CD34^{-}, CD56^{-}, TCRαβ^{-}, TCRγδ^{-}, TdT$^{-/+}$, CD1a^{-}, and HLA-DR^{-}. **b** May-Giemsa staining reveals medium-sized abnormal cells with delicate chromatin, distorted nuclei, and conspicuous nucleoli. **c–j** Pathological analysis of cell block specimen. Hematoxylin–eosin staining (**c**) shows monotonous proliferation of medium-sized abnormal lymphoid cells with fine nuclear chromatin and irregularly shaped nuclei. Using immunohistochemistry, they are cytoplasmic CD3^{+} (**d**), CD4^{-} (**e**), and CD8^{+} (**f**). TdT is only slightly positive overall, with sporadic strong positivity (**g**). On the other hand, the cells are positive for CD99 (**h**) and CD79a (**i**). Ki-67 index is 80% (**j**)

and conspicuous nucleoli (Fig. 1b). Pathological evaluation of the CSF cell block specimen revealed monotonous proliferation of medium-sized abnormal lymphoid cells with fine nuclear chromatin and irregularly shaped nuclei (Fig. 1c). Immunohistochemistry showed cytoplasmic $CD3^+$ (Fig. 1d), $CD4^-$ (Fig. 1e), and $CD8^+$ (Fig. 1f). TdT was only slightly positive overall, with sporadic strong positivity (Fig. 1g). The abnormal cells showed strong postivity for CD99 (Fig. 1h), supporting the immature phenotype [4]. They were also aberrantly positive for CD79a (Fig. 1i), which are characteristic of an early stage of T-cell differentiation [5]. However, the positivity for CD8 ruled out the possibility of early T-cell precursor T-ALL diagnosis, by definition. These abnormal cells tested negative for cytotoxic molecules such as TIA-1 and granzyme B, and Epstein–Barr virus-encoded RNA (in situ hybridization analysis). Ki-67 index was 80% (Fig. 1j). G-band analysis revealed a complex karyotype: 46,XY,add(1)(q12),add(9)(p24),del(9)(p13). Therefore, the patient was diagnosed with aleukemic T-ALL/LBL with massive CSF infiltration.

The was immediately treated with intravenous high-dose methotrexate (1 g/m^2, on day 1) and cytarabine (2 g/m^2 q 12 h, on days 2–3), combined with intrathecal injection of methotrexate (15 mg), cytarabine (40 mg), and dexamethasone (3.3 mg), four times within 3 weeks. This markedly reduced abnormal cells in the CSF. The patient's condition improved, and he was able to move as his symptoms subsided. He was, subsequently, transferred to another hospital in his hometown for further treatment.

Discussion

Approximately, 10% of T-ALL/LBL cases in adults are complicated with CNS infiltration at initial diagnosis [6, 7]. Although increased white blood cell count, T-cell immunophenotype, and presence of a mediastinal mass are associated with CNS disease at ALL presentation [7], aleukemic presentation with massive CNS infiltration is rare. The pathological factors associated with CNS infiltration of T-ALL/LBL remain unknown. It has been recently reported that CD79a promotes CNS infiltration in pediatric B-cell precursor ALL [8]. However, there have been no data showing a similar tendency of CD79a-positive T-ALL/LBL.

To our best knowledge, only two aleukemic T-ALL/LBL cases with exclusive CNS infiltration have been documented in the literature. The detailed clinicopathological information of these cases and the present case are summarized in Table 1. All three patients were young male patients, presented with progressive deterioration in various neurological symptoms, including headache, and MRI revealed contrast enhancement of the leptomeninges and/or cauda equina. Various differential diagnoses were initially considered, such as infectious meningoencephalitis, noninfectious inflammatory diseases, and demyelinating diseases. CSF analysis revealed massive infiltration of T-lymphoblasts (more than 1000/μL in CSF). Furthermore, CSF pathological analysis led to establishing a diagnosis of T-ALL/LBL. In one case, invasion into the cerebral parenchyma was confirmed. Bone marrow analysis revealed no leukemic cells in all cases. No systemic lesions were detected in the two previously reported cases. However, a mediastinal mass was observed in the present case. Elevated serum LDH levels were observed in one case, which could indicate insidious and patchy involvement of the bone marrow. Of note, CT showed mildly increased density in some bone marrow in the present case. Recognizing such a rare clinicopathological presentation of T-ALL/LBL is important because the symptoms could resemble that of other neurological diseases. Furthermore, a delay in CSF examination and therapeutic intervention could lead to unpreventable death or critical neurological sequelae. Sustained remission was achieved in the reported cases with a combination of systemic chemotherapy, intrathecal chemotherapy, and radiation therapy.

Patients with ALLwho present with initial CNS involvement have a poorer prognosis than do those without CNS disease [2, 9], partially due to higher CNS relapse rates [9]. Regarding ALL cases accompanied by overt CNS leukemia, intrathecal chemotherapy combined with systemic induction chemotherapy is recommended [3]. In addition, intensified intrathecal chemotherapy with methotrexate could also reduce CNS relapse and improve prognosis [10, 11]. Among various chemotherapy regimens, drugs that can cross the blood–brain barrier, such as high-dose methotrexate and cytrabine, are incorporated into consolidation therapy for CNS prophylaxis [3]. In the present case, prompt eradication of leukemic cells in the CSF was an urgent issue. Therefore, we administered intensified intrathecal chemotherapy and simultaneous intravenous high-dose methotrexate and cytarabine as induction therapy, resulting in favorable disease control. Allogeneic hematopoietic stem cell transplantation might also be a treatment option for sustained remission, as in the abovementioned case [12] and other refractory T-cell lymphoma cases [13, 14]. However, further clinical experience is required to establish treatment of aleukemic T-ALL/LBL with massive CNS infiltration from a practical standpoint.

In summary, we herein report an exceptional case presentation of aleukemic T-ALL/LBL with massive CSF infiltration, which was rescued by urgent intravenous and intrathecal chemotherapeutic intervention. Accumulation of similar cases is required for elucidating clinicopathological features and development of therapeutic strategies.

Table 1 Reported cases of aleukemic T-ALL/LBL with exclusive CNS infiltration

Reference	Age/sex	Symptoms	Duration of symptoms	Abnormal findings with MRI of brain and spine	CSF cell count (/μL)	Immunophenotype	Serum LDH (U/L)	Lesion sites other than CNS	Leukemic cells in peripheral blood and bone marrow	Treatment and outcome
Mazur et al. [12]	12/M	One-sided weakness, nausea, vomiting, headache, blurred vision, diplopia	ND	Several hyperintensity areas, heterogeneous CE of the leptomeninges	1790	$CD3^+$, $CD5^+$, $CD7^+$, $CD8^+$, $CD56^+$, $TCR\gamma\delta^+$, TdT^+, $CD1a^-$, $CD34^-$, $CD99^-$	ND	No other lesions	Examined but not detected	ChemoTx (incl. HD-MTX), IT, RT, alloHCT ➔Alive without disease 1 year after the initial presentation
Elavarasi et al. [15]	32/M	Fever, headache, neck pain, photophobia, phonophobia, lower limb heaviness, sensory disturbance, urinary retention	25 days	Leptomeningeal CE, thickening and CE of cauda equina nerve roots	3200	ND[a]	600	No other lesions	Examined but not detected	ChemoTx (hyperC-VAD), IT, RT ➔Alive without disease[b]
This case	19/M	Headache, neck pain, nausea, dysphagia, dizziness, difficulty in walking	1 month	Slight CE of cauda equina	2192	$sCD3^-$, $cyCD3^+$, $CD4^-$, $CD5^{dim+}$, $CD7^+$, $CD8^{dim+}$, $CD56^-$, $TCR\alpha\beta^-$, $TCR\gamma\delta^-$, $TdT^{-/+}$, $CD1a^-$, $HLA\text{-}DR^-$, $CD34^-$, $CD79a^+$, $CD99^+$	237	Mediastinal mass	Examined but not detected	ChemoTx (HD-MA), IT ➔Remission of disease

alloHCT, allogeneic hematopoietic stem cell transplantation; *ChemoTx*, systemic chemotherapy; *CE*, contrast enhancement; *cyCD3*, cytoplasmic CD3; *HD-MA*, high-dose methotrexate and cytarabine; *HD-MTX*, high-dose methotrexate; *hyperCVAD*, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; *IT*, intrathecal chemotherapy; *LDH*, lactic dehydrogenase; *M*, male; *MRI*, magnetic resonance imaging; *ND*, not described; *RT*, radiation therapy; *sCD3*, surface CD3

[a]The authors mention that the diagnosis of T-ALL/LBL is determined by flow cytometry and immunohistochemical analysis. Detailed information on this is not provided

[b]The duration of follow-up is not documented

Declarations

Conflict of interest The authors declare no competing interests.

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