Primary Cerebral Angioimmunoblastic T-Cell Lymphoma

Case Report

A 71-year-old woman with a past medical history of chronic alcoholism and depression presented with a subacute confusional state and was admitted to the Department of Neurology (Hôpital Pierre Wertheimer, Bron, France) in November 2008. At admission, the patient was somnolent, apathetic, and confused. Her spatiotemporal orientation and cognitive function were impaired. She suffered from a moderately painful headache but presented no meningeal syndrome. An initial neurologic examination was performed, which did not reveal any focal abnormality or cranial nerve palsy. A general examination of the patient was normal except for weight loss and a low-grade fever (38.3°C), which disappeared in time. No peripheral lymphadenopathy, splenomegaly hepatomegaly, and/or rash were noted. The patient had a WHO performance status of 3. All laboratory tests results, including C-reactive protein levels, lactate dehydrogenase levels, and CBC, were normal. HIV testing was negative. A diagnosis of metabolic alcohol- or drug-related disorders was rejected.

Brain computed tomography (CT) revealed extensive hypodensity in the right temporal lobe. Brain magnetic resonance imaging (MRI) revealed hyperintense lesions in the right temporal lobe on T2-weighted fluid-attenuated inversion recovery sequences (Fig 1A) and diffusion-weighted sequences. After gadolinium injection, the signal was enhanced in the lesion periphery, which suggested the presence of mild edema (Fig 1B). MRI also revealed leptomeningeal contrast enhancement in the right temporal region. Some lesions were also detected in the contralateral insular cortex.

CSF analysis revealed high total protein levels (1.37 mg/L), a normal CSF-to-serum glucose ratio, and increased cellularity (42 cells/μL) with pleocytosis (lymphocytes, lymphoplasmacytic cells, and plasma cells). No atypical cell or infectious agent was identified. Oligoclonal immunoglobulin G bands were present.

Because of a strong suspicion of herpes simplex virus meningoencephalitis, an intravenous administration of acyclovir was initiated. However, no herpes simplex virus DNA was detected in the CSF by polymerase chain reaction (PCR), and this treatment was stopped. The results of a full infection screening of the serum and CSF by PCR were negative, except for Epstein-Barr virus (EBV) DNA in the CSF (3.0 log copies/mL). The results of the immunologic tests were also negative. An electroencephalogram revealed an irregular diffuse abnormal slow-wave activity. After stimulation, an asymmetrical activity of periodic biphasic waves, which were clearly predominant over the right hemisphere, was observed. Contrast-enhanced CT of the chest, abdomen, and pelvis was normal and did not indicate the presence of a malignant tumor. Combined CT and [18F]fluorodeoxyglucose (FDG) positron emission tomography (PET) was performed 4 days after the brain MRI (Fig 2). Axial and coronal slices of FDG PET revealed a hypermetabolic focus (Fig 2, arrows) in the right temporal lobe that corresponded to known brain lesions. No extracerebral abnormality was identified. Bone marrow aspiration did not show infiltration by lymphoma or any other neoplastic disease. The dilated eye examination, including a slit-lamp evaluation, was normal.
One week later, the patient presented with left-sided neglect without hemiparesis and grasping deficit. Diplopia as a result of bilateral adduction limitation, right-eye exotropia, and anisocoria with right mydriasis were also noted. A second MRI was performed, which showed that the lesions extended to the left temporal lobe, bilateral frontobasal areas, insular cortex, and cingulate gyrus. Moreover, the leptomeningeal and gadolinium-enhanced lesions had worsened. An increased choline:creatine ratio, decreased N-acetyl aspartate level, and lipid peak were observed with proton magnetic resonance spectroscopy (Fig 3). A second CSF analysis was performed that revealed similar results to the previous ones, with persistent pleocytosis, hyperproteinorachia, and positive EBV PCR (3.0 log copies/mL).

A neuronavigation-guided stereotactic biopsy of the right temporal lesion was performed on December 1, 2008, which showed a diffuse polymorphic infiltrate of a mixed population of small-sized lymphocytes, plasma cells, histiocytes, and immunoblasts (Fig 4; EBER, EBV-encoded RNA). This infiltrate was prominent around small cerebral vessels. Immunohistochemistry showed a majority of CD3+ T cells, with a CD4+/CD10+/bcl-6+ phenotype. Few CD20+ B cells and numerous CD138+ plasma cells were spotted. Perivascular CD30+ immunoblasts were detected, and some of them expressed EBV-encoded RNAs. PCR analysis with BIOMED-2 primers was performed on frozen brain biopsy samples and revealed a clonal TCRγ gene rearrangement and minor clonal immunoglobulin heavy chain variable region rearrangement. A diagnosis of cerebral angioimmunoblastic T-cell lymphoma (AITL) was established.

The chemotherapy regimen consisted of three cycles of methotrexate, procarbazine, and vincristine (intravenous methotrexate 3.5 g/m² per day on days 1 and 15, intravenous vincristine 1.4 mg/m² per day on days 1 and 15, oral procarbazine 100 mg/m² per day for 7 days, and prednisolone 60 mg per day for 5 days). Because of the presence of a monoclonal B-cell population in the tumor and the positive CSF EBV load, immunotherapy with rituximab 375 mg/m² per day was coadministered on days 1 and 15 of the three cycles. The treatment was concluded with two cycles of high-dose cytarabine (3 g/m² per day for 2 days). The clinical and neurologic status of the patient improved during the first cycle of therapy. No treatment-related toxicity was observed. A serial evaluation of cognitive function was performed and showed an improvement in mental status; the result of the Folstein and Folstein Mini-Mental State Examination was nine of 30 points before chemotherapy, 24 of 30 points after 2 months, and 28 of 30 points at the end of the
treatment. MRI staging after two cycles of rituximab plus methotrexate, procarbazine, and vincristine confirmed the absence of a pathologic gadolinium-enhanced lesion on T1-weighted images. Axial and coronal slices of FDG PET performed simultaneously revealed a large photopenic area in the right temporal lobe (Fig 5, arrows; Gado, gadolinium enhanced), which was consistent with a complete metabolic response. A complete remission was achieved and was still sustained after 30 months with total recovery of cognitive function and complete normalization of neurologic examination.

**Discussion**

Primary CNS lymphoma (PCNSL) is a rare disease that affects the brain and possibly the meninges, eyes, cranial nerves, and spinal cord.\(^1\) PCNSL represents 4% of all brain tumors, 95% of which are diffuse large B-cell lymphomas. Others histologic types are rare and have mostly been described in retrospective series.\(^2,3\) A series of 45 PCNSLs of T cell-origin was described in 2005.\(^4\) In the study, 25 cases were pathology reviewed mainly with the description of the size of the tumor cell. Immunohistochemistry had been performed in all except three cases and showed positivity to CD3, CD4, or CD45RO markers; 13 cases had features of a T-cell anaplastic lymphoma with coexpression of CD30 and CD3. In addition to this large series, several case reports of T-cell PCNSL were found in the literature. However, none of them described the features of AITL.\(^5\) In the current case, some of the characteristic features of a PCNSL were noted, especially the aspect of an angiocentric tumor.\(^1\) The morphology and immunohistochemistry results were in accordance with a diagnosis of AITL because of the presence of T cells with a typical T-follicular helper cell immunophenotype and the presence of EBV-infected B immunoblasts. Moreover, clonal T-cell receptor \(\gamma\) and immunoglobulin gene rearrangements were detected, which have been observed in approximately 30% of AITL cases.\(^6\) Unfortunately, we could not research recurrent cytogenetic abnormalities, such as trisomy 3, 5, or the gain of an X chromosome.

Regarding the clinical presentation, initial staging did not reveal any systemic localization confirmed by PET-CT and did not reveal any bone marrow involvement, which is frequent in AITL. In addition, the patient did not present any constitutional symptoms, polyarthritis, or arthralgia and did not present any cutaneous
symptom, which could have suggested a diagnosis of AITL. The initial neurologic symptoms of the patient were unspecified and similar to those of other brain tumors, although neuroimaging data were consistent with the features of PCNSLs.7 The laboratory findings confirmed no autoimmune phenomenon and a normal serum protein electrophoresis.

In the large AITL series reported in the literature, there was no patient with initial brain parenchyma involvement.8-13 The most frequent neurologic manifestations described in AITL are peripheral neuropathies.14-16 In a recent series, eight of 77 patients (10%) presented neurologic symptoms at the time of AITL diagnosis, and two of them had tumor cells in the CSF.9 In another series of 33 patients, one patient had CSF involvement.11

A regimen with high-dose methotrexate and cytarabine17 without radiotherapy allowed for the maintenance of a complete response for at least two years after diagnosis. Some authors suggested treating rare T-cell PCNSL with a similar approach to that used for patients with a B-cell PCNSL, and the outcome seems to be similar.2 In the current case, an anti-CD20 monoclonal antibody was also used to target EBV-infected clonal B cells. Indeed, objective responses were observed with monotherapy with the anti-CD20 monoclonal antibody for recurrent B-cell PCNSLs,18 and rituximab was also evaluated in combination with chemotherapy in AITLs on the basis of their pathogenesis, which indicated the presence of CD20+ immunoblastic B cells.19

The question remains regarding the origin of the tumor cells found in the brain because T-follicular helper cells are localized within germinal centers.6 In our patient, no circulating lymphomatous cells were detected by blood smear analysis, although these can be found in approximately 30% of patients with AITL.9 Unfortunately, we could not perform a search for clonal disease associated with a brain-tumor T-cell clone by using blood or bone marrow samples. In the rare cases of T-cell PCNSL, extensive morphologic, immunophenotypic, and genetic studies should be performed to understand better and with more accuracy the entities that comprise T-cell lymphomas, such as AITL. In addition, in case of systemic AITL, a systematic CNS exploration should be performed to clarify the mechanism of this lymphoma toward the CNS.

Fig 4.
AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

REFERENCES

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