Case Report

A case of large B-cell intravascular lymphoma in the brain

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Abstract

Background: Intravascular lymphoma is a rare and fatal disease that can have central nervous system (CNS) manifestations. It is usually a diagnosis made postmortem. This is partly due to its varied presentation, which lends itself to the complexity of diagnosis.

Case Description: We report a rare case of intravascular lymphoma in the brain found antemortem.

Conclusion: Review of the literature shows that a timely diagnostic tissue biopsy together with aggressive combination chemotherapy treatment can improve patient outcome.

Key Words: B-cell, brain tumor, intravascular lymphoma

INTRODUCTION

Intravascular lymphoma (IVL) is an uncommon and usually fatal disease distinguished by the intraluminal proliferation of lymphoma cells within blood vessels.[3,5,30] The lymphoma cell proliferation is absent in the surrounding tissue parenchyma, lymph nodes and bone marrow; the latter two being sites typically affected in classical lymphoma.[21]

According to the World Health Organization (WHO), IVL has been classified as a form of diffuse large B-cell lymphoma (DLBCL),[15] though cases with a T-cell receptor phenotype have been reported.[8] Though any organ can be involved, IVL has been known to commonly affect the brain and skin.[16,20] The pattern of brain involvement usually manifests as subacute encephalopathy, dementia, seizures, or multifocal cerebrovascular events.[14,7,19] However, because of the variability of clinical presentation and the lack of diagnostic protocols available, approximately half of IVL cases are diagnosed only after autopsy.[11] Many of the antemortem diagnoses of IVL are rare and incidental findings in biopsies performed initially for different purposes.

Here we present an antemortem case of IVL in the brain.

CASE REPORT

A 59-year-old businessman, with a background of hypertension, dyslipidemia and diet-controlled Type II diabetes, initially presented to our institution in January 2010 with acute confusion. Prior to presentation he had been experiencing headaches and seizures for a month. Computed tomography (CT) scan of the brain showed no evidence of intracranial hemorrhage or infarct. Given the patient’s history of recent air travel, a CT pulmonary angiogram was done. This showed a nonocclusive subsegmental embolus within the left anteromedial basal artery. He was treated accordingly and subsequently discharged.
Four days later the patient suffered another seizure while sitting at his computer, followed by postictal drowsiness lasting 2 hours. Repeat CT scan was normal. Magnetic resonance imaging (MRI) showed subacute ischemia in the left frontal deep white matter, a small lacunar infarct in the left parietal white matter and a hypoplastic left transverse sinus. The possibility of cortical vein thrombosis was considered, given the patient’s presentation with seizures and pulmonary embolism. He was therefore started on phenytoin and warfarin.

The patient subsequently developed acute confusion. A MRI [Figure 1] was repeated, which showed multiple hemorrhagic foci in bilateral cerebral hemispheres, with perilesional edema and mild mass effect. Urgent electroencephalography (EEG) showed mild diffuse encephalopathy but no seizure activity. Differential diagnoses were infection, tumor, or recent hematoma. Blood tests showed anemia (hemoglobin 10.3 g/dL) with elevated lactate dehydrogenase (LDH) of 667 U/L. CT scans of the thorax, abdomen, and pelvis were normal as was the septic screen. Syphilis and human immunodeficiency virus (HIV) testing were negative.

The anticoagulation was reversed. However, the patient’s mental status deteriorated further 2 days later. His preoperative Karnofsky performance status (KPS) score was 50. An urgent CT scan [Figure 2] revealed an increase in size of multiple scattered hypodense lesions involving the deep white and subcortical matter in both cerebral hemispheres compared with the recent MRI. There were also tiny hyper densities seen within the right superior parietal lobe lesion likely representative of acute bleeding.

The patient was then brought to the operating theatre for decompression of what was thought to be related to a tumor bleed. Intraoperatively, there was extensive brain edema. A right occipital lobectomy revealed an intravascular large B-cell lymphoma. The blood vessels of the leptomeninges, cerebral cortex and white matter demonstrated multifocal occlusion by large lymphoid cells with pleomorphic nuclei, prominent nucleoli and mitotic activity [Figure 3a and Figure 4]. The intraluminal lymphoid cells showed

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**Figure 1:** MRI demonstrating multiple hemorrhagic foci in bilateral cerebral hemispheres.

**Figure 2:** CT scan demonstrating increase in multiple hypodensities in bilateral cerebral hemispheres.

**Figure 3a:** A leptomeningal vessel showing luminal occlusion by large pleomorphic lymphoma cells (H&E × 200)

**Figure 3b:** CD20 stains the intraluminal tumour cells (CD20 × 200)
strong expression of the B lymphocyte marker C20 by immunoperoxidase staining [Figure 3b]. Ki67 labeled the majority of the atypical lymphoid cells [Figure 3c]. The T lymphocyte marker CD3 showed reactive perivascular T lymphocytes. Some of the tumor cells appeared to extend into the walls of the blood vessels. There was otherwise no extravascular proliferation identified in the tissue submitted. There was astrogliosis and focal hemorrhagic infarction of the cerebral parenchyma.

The patient had an uneventful postoperative course, with his KPS score as 60 and was transferred to the medical oncology service for further management.

A pretreatment positron emission tomography (PET) scan showed uptake in periventricular white matter, left parietal white matter, left occipital para-median cortex, and right hemi-midbrain. There was also diffuse uptake in the spleen and bone marrow. Trephine biopsy of the marrow revealed no lymphomatous involvement. He was commenced on chemotherapy with rituximab–cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and high dose intravenous (IV) methotrexate in early February 2010. PET scans post 4 and 6 cycles showed no evidence of metabolically active disease in the areas of uptake shown in the pretreatment scan. He completed 6 cycles of chemotherapy in total, followed by 30 Gray (Gy) of whole brain radiotherapy given in 15 fractions.

On follow-up the patient was able to walk with support although still left with a dense left homonymous hemianopia, which was documented prior to starting chemotherapy. His KPS score was 40. The patient remained in clinical remission for about 24 months since the original diagnosis of IVL was made, only to relapse with multiple myeloma in June 2012 when he presented with symptoms of cauda equina syndrome secondary to a sacral mass. CT guided biopsy of the sacral mass revealed spinal plasmacytoma. The patient subsequently passed away from pneumonia.

DISCUSSION

Previously termed as ‘angioendotheliomatosis proliferans systemisata’,[24] IVL is an uncommon and generally terminal disease involving intraluminal proliferation of non-Hodgkin lymphoma cells in blood vessels. Current literature shows that IVL tends to affect elderly patients in the 6th to 7th decades of life, with a male-to-female ratio of 1:2. It has been suggested that the incidence of IVL is increased in Asian populations, such as an IVL variant associated with hemophagocytosis.[23] However, this may be due to increased awareness of this disease in Japan.[23] At present there are no established predisposing risk factors for IVL, though several cases of IVL associated with DLBCL[31] and follicular lymphoma[6] have been reported.

The majority of cases of IVL are extremely varied in presentation and have been described in the vessels of nearly every body organ. Usual sites of involvement are the brain and skin[16,28] manifesting as diffuse encephalopathy, subacute progressive neurological deficits, cutaneous involvement or fever of unknown origin.[4,7,19] One series of IVL reported 13 of 38 patients presenting with neurologic symptoms either exclusively or as associated symptoms.[13] Initial diagnoses considered are usually stroke, encephalomyelitis, Guillain–Barré syndrome, vasculitis, and multiple sclerosis, and it is not uncommon that the diagnosis of IVL is made at autopsy.[4,14,16,20] MRI has been shown to be the best modality of imaging for IVL despite its low level of sensitivity and specificity. Abnormalities such as multiple hyperintense cortical or subcortical lesions found on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging suggest small vessel ischemia or demyelination changes.[12,29] Other differentials involving such MRI findings include central nervous system (CNS) vasculitis.[6,20] In a series of IVL patients with CNS disease, it was found that six of seven patients had cerebrospinal fluid (CSF)
lymphocytosis, although only one of seven patients had CSF malignant cytopathology. Two of the seven patients had malignant cells analyzed by polymerase chain reaction (PCR) for IgH gene rearrangement. In terms of laboratory findings, the most common abnormalities observed in IVL are anemia (63% of cases), high LDH (82%) and b-2-microglobulin serum levels (86%). Thrombocytopenia and leucopenia are less common (24% and 29%, respectively). Bone marrow infiltration has been reported in only 35% of cases. It is uncommon (5%) to see circulating neoplastic cells on the peripheral blood smear.

The unpredictability of clinical presentation and the lack of diagnostic protocols available have resulted in approximately half of IVL cases being diagnosed only after autopsy. In fact many of the antemortem diagnoses of IVL are made incidentally in biopsies performed for different reasons. This low incidence of antemortem diagnosis points to the importance of a timely tissue biopsy, which is a generally safe procedure. A low threshold should always be maintained to biopsy abnormal brain or skin lesions, and care should be taken to obtain multiple biopsies due to the presence of focal localization in IVL. In our case, we had a large occipital lobectomy specimen following the patient’s clinical deterioration, which warranted urgent surgical intervention. In retrospect, we would have had planned to do an early biopsy after excluding more common presentations such as cerebral ischemia or cerebral venous thrombosis. The clinical course of IVL has been shown to be an aggressive one and most cases are associated with a poor prognosis. Data in the literature indicates that IVL should be treated systemically with an anthracycline-based regimen such as R-CHOP. In a series conducted by the International Extranodal Lymphoma Study Group involving 22 participants, 19 received an anthracycline-based regimen with a response rate of 59% (10 complete remissions, 3 partial responses). However, seven of the participants eventually relapsed. The three patients treated with cyclophosphamide, vincristine, and prednisone (CVP) relapsed, although one had a late spontaneous remission. A separate study conducted by John Hopkins Hospital found that 4 of the 10 patients who received combination chemotherapy (3 CHOP and 1 Pro-MACE-CytaBOM [cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, and prednisone]) achieved complete remission and were alive at the time of follow-up (6–48 months). It also has been observed that patients with evidence of IVL within the CSF are not likely to respond to R-CHOP because of its poor penetration of the blood–brain barrier, and they should be treated with regimens similar to those used in primary or secondary CNS lymphoma.

Intrathecal or high-dose systemic methotrexate should be included. Both high-dose corticosteroids (up to 1 g daily of methylprednisolone) and plasmapheresis have been described as providing temporary benefit, but without sustained therapeutic efficacy. Without treatment IVL has a 1-year mortality rate approximating 80% from the time of diagnosis, and an average survival rate of about 13 months. It is crucial to obtain an early diagnosis as IVL may be curable with appropriate chemotherapy. The prognosis of IVL is greatly improved with combination chemotherapy and early diagnosis, with a complete remission rate of about 42% that can allow for long-term survival. This result is comparable to other conventional lymphomas.

**CONCLUSION**

IVL is a disease of the elderly with an aggressive clinical course if left untreated. Its myriad of clinical presentations and lack of pathognomonic features or markers have made antemortem clinical diagnosis difficult and challenging. Timely diagnosis and intervention with combination chemotherapy are important for a satisfactory patient outcome.

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