Case Report

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

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This article may be cited as:
Gan LP, Ooi WS, Lee HY, Ng WH. A case of large B-cell intravascular lymphoma in the brain. Surg Neurol Int 2013;4:99.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2013/4/1/99/115709

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.[16,28] The pattern of brain involvement usually manifests as subacute encephalopathy, dementia, seizures, or multifocal cerebrovascular events.[4,7,19] 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
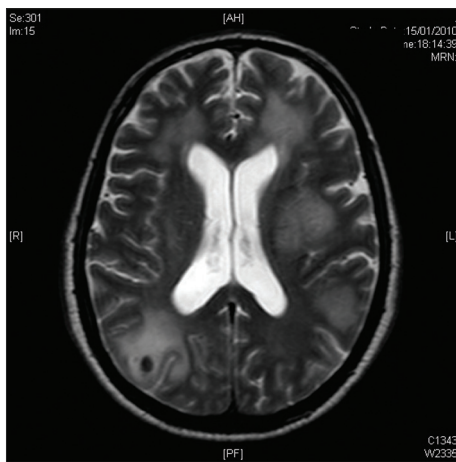

Figure 1: MRI demonstrating multiple hemorrhagic foci in bilateral cerebral hemispheres.

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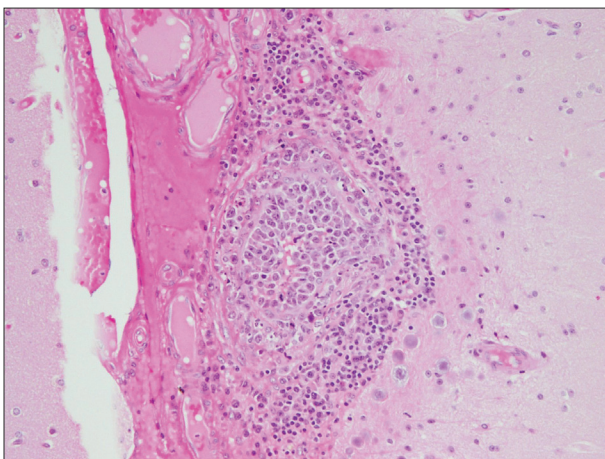

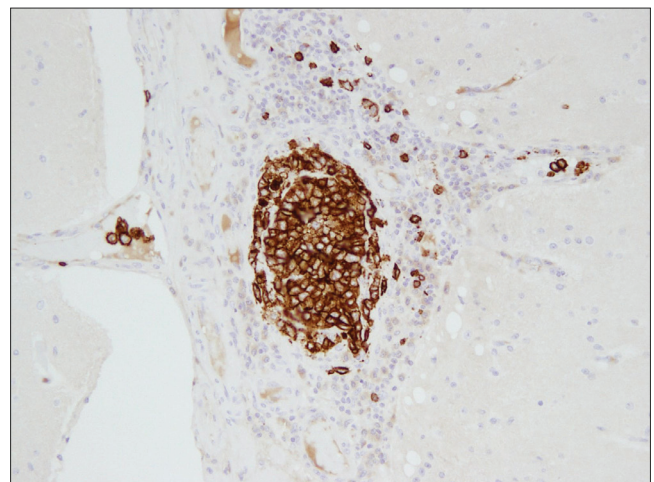Figure 3a: A leptomeningeal vessel showing luminal occlusion by large pleomorphic lymphoma cells (H&E × 200)

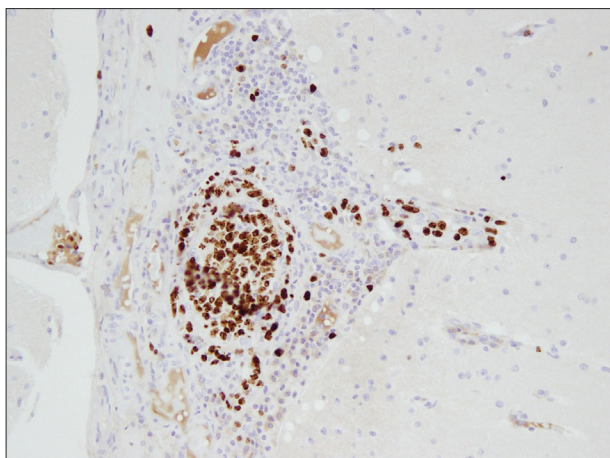Figure 3b: CD20 stains the intraluminal tumour cells (CD20 × 200)

Figure 3c: The proliferative marker Ki-67 labels majority of the intraluminal tumor cells (Ki67 × 200)

Figure 4: White matter with vessels showing luminal occlusion by lymphoma cells (H&E × 400)

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.
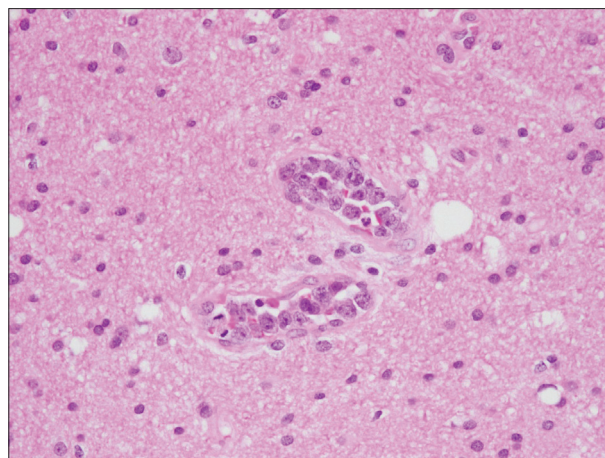
DISCUSSION

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.[4,14,18,20]

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.[1,29] Other differentials involving such MRI findings include central nervous system (CNS) vasculitis.[4,20]

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.[1]

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).[13] Bone marrow infiltration has been reported in only 38% of cases.[13] It is uncommon (5%) to see circulating neoplastic cells on the peripheral blood smear.[2,25]

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.[11] 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,[32] 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.[13] Data in the literature indicates that IVL should be treated systemically with an anthracycline-based regimen such as R-CHOP.[12] In a series conducted by the International Extranodal Lymphoma Study Group involving 22 participants,[12] 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 organized 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).[10]

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.[32]

Intrathecal or high-dose systemic methotrexate should be included.[9] 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.[7,17]

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.[22] It is crucial to obtain an early diagnosis as IVL may be curable with appropriate chemotherapy.[26] 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.[10,27] 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.

REFERENCES

1. Baehring JM, Longtine J, Hochberg FH. A new approach to the diagnosis and treatment of intravascular lymphoma. J Neurooncol 2003;61:237-48.
2. Bazhenova L, Higginbottom P, Mason J. Intravascular lymphoma: A role for single-agent rituximab. Leuk Lymphoma 2006;47:337-41.
3. Bhawan J. Angioendotheliomatosis proliferans systemisata: An angiotropic neoplasm of lymphoid origin. Semin Diagn Pathol 1987;4:18-27.
4. Calamia KT, Miller A, Shuster EA, Perniciaro C, Menke DM. Intravascular lymphomatosis. A report of ten patients with central nervous system involvement and a review of the disease process. Adv Exp Med Biol 1999;455:249-65.
5. Carroll TJ, Schelper RL, Goeken JA, Kemp JD. Neoplastic angioendotheliomatosis: Immunopathologic and morphologic evidence for intravascular malignant lymphomatosis. Am J Clin Pathol 1986;85:169-75.
6. Carter DK, Batts KP, de Groen PC, Kurtin PJ. Angiotropic large cell lymphoma (intravascular lymphomatosis) occurring after follicular small cleaved cell lymphoma. Mayo Clin Proc 1996;71:869-73.
7. Chapin JE, Davis LE, Kornfeld M, Mandler RN. Neurologic manifestations of intravascular lymphomatosis. Acta Neurol Scand 1995;91:494-9.
8. Chen M, Qiu B, Kong J, Chen J. Angiotropic T cell lymphoma. Chin Med J (Engl) 1998;111:762-4.
9. Debiais S, Bonnaud I, Cottier JP, Destrieux C, Saudeau D, de Toffol B, et al. A spinal cord intravascular lymphomatosis with exceptionally good outcome. Neurology 2004;63:1329-30.
10. DiGiuseppe JA, Nelson WG, Seifter EJ, Boitnott JK, Mann RB. Intravascular lymphomatosis: A clinicopathologic study of 10 cases and assessment of response to chemotherapy. J Clin Oncol 1994;12:2573-9.
11. Domizio P, Hall PA, Cotter F, Amiel S, Tucker J, Besser GM, et al. Angiotropic large cell lymphoma (ALCL): Morphological, immunohistochemical and genotypic studies with analysis of previous reports. Hematol Oncol 1989;7:195-206.
12. Ferreri AJ, Campo E, Ambrosetti A, Ilariucci F, Seymour JF, Willemze R, et al. Anthracycline-based chemotherapy as primary treatment for intravascular lymphoma. Ann Oncol 2004;15:1215-21.
13. Ferreri AJ, Campo E, Seymour JF, Willemze R, Ilariucci F, Ambrosetti A, et al; International Extranodal Lymphoma Study Group (IELSG). Intra-

vascular lymphoma: Clinical presentation, natural history, management and prognostic factors in a series of 38 cases, with special emphasis on the 'cutaneous variant'. Br J Haematol 2004;127:173-83.

14.　Fredericks RK, Walker FO, Elster A, Challa V. Angiotropic intravascular large-cell lymphoma (malignant angioendotheliomatosis): Report of a case and review of the literature. Surg Neurol 1991;35:218-23.

15.　Gatter KC, Warnke RA. Intravascular large B-cell lymphoma. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. Tumours of Haematopoietic and Lymphoid Tissues, Vol. 1. Lyon: IARC Press; 2001. p. 177-8.

16.　Glass J, Hochberg FH, Miller DC. Intravascular lymphomatosis. A systemic disease with neurologic manifestations. Cancer 1993;71:3156-64.

17.　Harris CP, Sigman JD, Jaeckle KA. Intravascular malignant lymphomatosis: Amelioration of neurological symptoms with plasmapheresis. Ann Neurol 1994;35:357-9.

18.　Hsu YH, Tseng BY, Shyu WC, Yen PS. Intravascular lymphomatosis mimicking acute disseminated encephalomyelitis: A case report. Kaohsiung J Med Sci 2005;21:93-7.

19.　Lapkuviene O, Forchetti D, Roepke JE. Unusual sites of involvement by hematologic malignancies. Case 1. Intravascular large B-cell lymphoma presenting with CNS symptoms. J Clin Oncol 2001;19:3988-91.

20.　Legerton CW 3rd, Sergent JS. Intravascular malignant lymphoma mimicking central nervous system lupus. Arthritis Rheum 1993;36:135.

21.　Mann RB. Are there site-specific differences among extranodal aggressive B-cell neoplasm? Am J Clin Pathol 1999;111(Suppl 1):S144-50.

22.　Mock DJ, Jundt JW, Green JB, Speights VO. Angiotropic lymphoma manifested by fever and painful swollen legs. South Med J 1993;86:1432.

23.　Murase T, Nakamura S, Kawauchi K, Matsuzaki H, Sakai C, Inaba T, *et al.* An Asian variant of intravascular large B-cell lymphoma: Clinical, pathological and cytogenetic approaches to diffuse large B-cell lymphoma associ-ated with haemophagocytic syndrome. Br J Haematol 2000;111:826-34.

24.　Pfleger L, Tappeiner J. Zur Kenntnis des systemisierten Endotheliomatose der cutanen Blutgafaesse. Hautarzt 1959;10:359-63.

25.　Ponzoni M, Ferreri AJ. Intravascular lymphoma: A neoplasm of 'homeless' lymphocytes? Hematol Oncol 2006;24:105-12.

26.　Sanna P, Bertoni F, Roggero E, Quattropani C, Rusca T, Pedrinis E, *et al.* Angiotropic (intravascular) large cell lymphoma: Case report and short discussion of the literature. Tumori 1997;83:772-5.

27.　Shanks JH, Harris M, Howat AJ, Freemont AJ. Angiotropic lymphoma with endocrine involvement. Histopathology 1997;31:161-6.

28.　Sheibani K, Battifora H, Winberg CD, Burke JS, Ben-Ezra J, Ellinger GM, *et al.* Further evidence that "malignant angioendotheliomatosis" is an angiotropic large-cell lymphoma. N Engl J Med 1986;314:943-8.

29.　Vieren M, Sciot R, Robberecht W. Intravascular lymphomatosis of the brain: A diagnostic problem. Clin Neurol Neurosurg 1999;101:33-6.

30.　Wrotnowski U, Mills SE, Cooper PH. Malignant angioendotheliomatosis. An angiotropic lymphoma? Am J Clin Pathol 1985;83:244-8.

31.　Zhao XF, Sands AM, Ostrow PT, Halbiger R, Conway JT, Bagg A. Recurrence of nodal diffuse large B-cell lymphoma as intravascular large B-cell lymphoma: Is an intravascular component at initial diagnosis predictive? Arch Pathol Lab Med 2005;129:391-4.

32.　Zuckerman D, Seliem R, Hochberg E. Intravascular lymphoma: The oncologist's "great imitator". Oncologist 2006;11:496-502.