CASE REPORT

Intravascular lymphoma: an unusual cause of rapid cognitive decline and the role of brain biopsy

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SUMMARY

Intravascular lymphoma (IVL) is a rare extra nodal variant of non Hodgkin's lymphoma characterised by neoplastic lymphoid cells growing inside the lumina of medium and small vessels. IVL limited to the central nervous system (CNS) is an extremely rare condition as IVL is usually found with systemic lesions. Most cases of IVL are not diagnosed until post mortem because of variable clinical presentation and non-specific laboratory findings. Even if diagnosed early the disease is clinically aggressive and usually fatal, even with early detection and treatment. We present a case of a 37-year-old woman with a short history of behavioural abnormality, rapidly progressive cognitive decline and seizures. There were no cutaneous manifestations. Diagnosis was established only after the brain biopsy. The case is presented for the rarity of its presentation and role of brain biopsy in diagnosis.

BACKGROUND

The case is presented because intravascular central nervous system (CNS) lymphoma presenting as behavioural abnormality, cognitive decline and seizures is rare. It is also important to highlight the role of brain biopsy in the diagnostic approach to intravascular lymphoma (IVL) involving the CNS.

CASE PRESENTATION

A 37-year-old woman with symptoms of forgetfulness of recent events and behaviour changes for 2.5 months and generalised tonic-clonic seizures for 1.5 months was brought by her relatives. Her symptoms had started in an unusual manner with the patient making frequent mistakes while cooking, not dressing properly and being abusive with family members and neighbours. Gradually she was neither able to do her routine household chores properly nor take care of her own activities of daily living. Within a short span of 2.5 months she had become totally dependent on her family members. There were no other symptoms suggesting systemic involvement. On neurological examination, the patient was conscious but not following commands. There were no signs of meningeal irritation. Her speech output was decreased and incomprehensible. Cranial nerve examination did not reveal any abnormality and no focal motor deficit was observed. Deep tendon reflexes were exaggerated and planters were bilaterally flexor. Abdominal ultrasonogram showed splenomegaly. However, no hepatomegaly, lymphadenopathy or any other abnormality was noted on systemic examination. To summarise, clinical history and examination suggested the patient had a rapidly progressive

cognitive impairment with generalised tonic-clonic seizures. The patient was admitted and investigated to identify the aetiology of these rapidly progressive cognitive deficits.

INVESTIGATIONS

The patient's routine investigations on day 1 of admission showed no significant abnormality (haemoglobin (Hb) 12.8 g/dL, total leucocyte count (TLC) 6600/mm³, platelet 2.35 × 10⁹/L, erythrocyte sedimentation rate (ESR) 22 mm in first hour, serum glutamic oxaloacetic transaminase (SGOT) 38 U/L, serum glutamic pyruvic transaminase (SGPT) 42 U/L, γ-glutamyl transferase (GGT) 60 U/L). However the same investigations repeated on day 10 (Hb 10.8 g/dL, TLC 5510/mm³, platelet 1.76 × 10⁹/L, ESR 44 mm in first hour, SGOT 101 U/L, SGPT 100 U/L, GGT 779 U/L) and day 15 (Hb 10 g/dL, TLC 4000/mm³, platelet 1.2 × 10⁹/L, ESR 52 mm in first hour, SGOT 186 U/L, SGPT 107 U/L, GGT 1081 U/L) showed a pattern of developing pancytopenia with a concomitant rise of liver enzymes. Serum ferritin was 401 ng/mL, lactate dehydrogenase (LDH) was 420 IU/L while fibrinogen was 407 mg/dL. Blood urea and creatinine, serum uric acid and electrolytes were within normal range. Cerebrospinal fluid (CSF) examination was also performed (TLC 3/mm³; glucose of 68 mg/dL; Protein; 51 mg/dL; herpes simplex virus PCR, Gram's stain, India ink stain for *Cryptococcus* were all negative and no atypical cells were observed on microscopic examination of a cytocentrifuged deposit of CSF).

MRI on T2-weighted images showed bilateral asymmetrical diffuse white matter changes in parietal, temporal and frontal areas with restricted diffusion in the same areas (figure 1). Minimal enhancement was seen on contrast imaging. The radiological differential diagnoses of diffuse encephalitis and lymphoma were considered. EEG was also done, which showed the diffuse slowing.

The patient was managed empirically with antivirals and antiepileptics. However, her sensorium level and general condition kept worsening. As a last resort brain biopsy from the right frontal region was performed to rule out any treatable cause.

Formalin fixed biopsy pieces, together measuring 1.0 × 1.0 × 0.2 cm, were submitted for histopathology processing. Paraffin embedded sections, stained with H&E showed well preserved cortical and white matter areas. Except for small collections of perivascular lymphocytes at some foci, no significant pathology could be appreciated. However,

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Figure 1 T2-weighted axial MRI showing diffuse hyperintense lesions in bilateral frontal and parietal areas.

strikingly seen were medium and small calibre blood vessels completely stuffed with large round cells with prominent nucleoli and frequent mitotic figures (figure 2A). On immunostaining, these cells were found to be strongly positive for CD20 (figure 2B). These cells were not seen in extravascular locations. On the basis of the histopathological and immunohistochemical findings, diagnosis of intravascular large B-cell lymphoma was made.

TREATMENT

After the diagnosis of IVL on histopathology, the patient was treated with steroids and chemotherapy including cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP regimen).

OUTCOME AND FOLLOW-UP

Disease was rapidly progressive and the patient expired within 2 months of diagnosis

DISCUSSION

IVL, also known as angiotropic lymphoma, is a very rare non-Hodgkin's lymphoma with an estimated frequency of <1% of all lymphomas. It is characterised by proliferation of the large lymphoid cell (85–90% with B-cell phenotype) in the lumen of middle-sized and small-sized vessels.¹ IVL limited to the CNS is an extremely rare condition as IVL is usually found with systemic lesions.² Affected patients present with a variety of focal and non-focal CNS manifestations, including the consequences of occlusive vascular disease, subacute encephalopathy, dementia, spinal cord or nerve root symptoms and cranial neuropathies.³ Most cases of IVL are not diagnosed until post mortem because of variable clinical presentation and non-specific laboratory findings.⁴ Even if diagnosed early the disease is clinically aggressive and usually fatal, even with early detection and treatment.

Figure 2 (A) Microphotograph showing round tumour cells within the lumen of blood vessels (arrow; H&E ×400). (B) Tumour cells showing immunopositivity for CD20 (CD20 ×400).

While constitutional symptoms such as general fatigue and oedema as well as involvement of the CNS are common in all patients, involvement of skin is more common in patients in Western countries and involvement of the gastrointestinal tract is more common in Asian countries.⁵ IVL has a high tendency to be associated with haemophagocytic syndrome in Asian but not in Western patients.⁶ In our patient, though fibrinogen was near the normal range, the pattern of developing pancytopenia along with an increased LDH and ferritin level indicated haemophagocytosis. It is also known that around two-third of 200 cases reported so far presented with neurological disease, which reflects the phenomenon of vascular occlusion that characterises the disease. The four most frequently cited syndromes include multifocal cerebrovascular events, spinal cord and nerve vascular syndromes, subacute encephalopathy and cranial or peripheral neuropathies.⁷ Presentation with only rapid cognitive decline and seizures is, to the best of the authors' knowledge, rare. Also, our patient did not have any gastrointestinal or skin involvement or features suggestive of haemophagocytic syndrome.

Diagnosis of IVL may be difficult to perform when neurological symptoms are the only manifestations of the disease. It is difficult to diagnose ante-mortem because of its variable clinical presentation and non-specific laboratory findings.⁸ Neuroimaging findings are also non-specific and include mass lesions, infarcts with or without haemorrhagic transformation, and non-specific white matter lesions.⁹ Most of the more than 200 reported cases were diagnosed post mortem following

autopsy study.⁷ According to all mentioned data, diagnosis of CNS IVL requires a histopathological confirmation. Brain biopsy is absolutely indicated in patients with progressive neurological deterioration with unclear abnormalities in cerebral MRI. However, as can be anticipated, predictive value of a negative biopsy would remain low. It can be stated that diagnosis of IVL remains, at best, serendipitous. The clinical team should be alert and aware of the possibility and contemplate brain biopsy as part of the diagnostic armamentarium.

As far as treatment is concerned, a general policy is that patients with IVL should be considered to have disseminated disease and should be treated with systemic chemotherapy. In younger patients with unfavourable features, high-dose chemotherapy with autologous stem cell transplantation should be used. Nevertheless, the course of IVL is rapidly progressive and ultimately fatal.¹⁰

The case report highlights the possibility of IVL in a clinical setting of rapid cognitive decline and the relevance of biopsy in the diagnostic approach.

Learning points

- ▶ Intravascular lymphoma should be considered in the setting of rapid cognitive decline.
- ▶ Brain biopsy has a role to play especially when radiology is unremarkable.
- ▶ Immunohistochemistry is an important diagnostic aid in interpreting the brain biopsy findings.

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REFERENCES

- 1 Renjen PN, Kjan NI, Gujrati Y, *et al.* Intravascular large B-cell lymphoma confirmed by brain biopsy: a case report. *BMJ Case Rep* 2013;2013:pii:bcr2012007990.
- 2 Momota H, Narita Y, Miyakita Y, *et al.* Intravascular Lymphoma of the central nervous system presenting as multiple cerebral infarctions. *Nagoya J Med Sci* 2012;74:353–8.
- 3 Burger Peter C, Scheithauer Bernd W, Vogel Stephen F. *Surgical pathology of the nervous system and its coverings*. 4th edn. Philadelphia, PA: Churchill Livingstone, 2002:324.
- 4 Liew CL, Shyu WC, Tsao WL, *et al.* Intravascular lymphomatosis mimicks a cerebral demyelinating disorder. *Acta Neurol Taiwan* 2006;15:264–8.
- 5 Shimada K, Kinoshita T, Naoe T, *et al.* Presentation and management of intravascular large B cell lymphoma. *Lancet Oncol* 2009;10:895–902.
- 6 Fung KM, Chakrabarty JH, Kern WF, *et al.* Intravascular large B-cell lymphoma with hemophagocytic syndrome (Asian variant) in a Caucasian patient. *Int J Clin Exp Pathol* 2012;5:448–54.
- 7 Aznar AO, Montero MA, Rovira R, *et al.* Intravascular large B-cell lymphoma presenting with neurological syndromes: clinicopathologic study. *Clin Neuropathol* 2007;26:180–6.
- 8 Liew CL, Shyu WC, Tsao WL, *et al.* Intravascular lymphomatosis mimicks a cerebral demyelinating disorder. *Acta Neurol Taiwan* 2006;15:264–8.
- 9 Martin DN, Mokhtar K, Behin A, *et al.* Intravascular malignant lymphomatosis. *Neuroradiology* 2002;44:749–54.
- 10 Mihaljevic B, Sternic N, Skender Gazibara M, *et al.* Intravascular large B-cell lymphoma of central nervous system—a report of two cases and literature review. *Clin Neuropathol* 2010;29:233–8.

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