

Brain Biopsy-Proven Intravascular Lymphomatosis Presenting as Rapidly Recurrent Strokes-Two Case Reports

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Abstract

Purpose: Intravascular lymphomatosis (IVL) is rare and usually goes undiagnosed until the time of autopsy because of its protean neurological manifestations.

Case Report: In this report, we describe two women who developed rapidly recurrent strokes within one to two months. In both cases, brain magnetic resonance imaging showed progression of bilateral cerebral infarcts, and histopathology from brain biopsy confirmed the diagnosis of IVL. The first case did not receive chemotherapy and died of septic shock one month after diagnosis. The second case received whole brain radiotherapy followed by rituximab-containing chemotherapy, and experienced partial improvement of neurological deficits. However, she began to deteriorate in consciousness at 8 months and became stuporous at 10 months after the onset of symptoms.

Conclusion: IVL should be considered as a possible etiology if multiple strokes occur in a short period of time.

Key Words: intravascular large B-cell lymphoma, intravascular lymphomatosis, ischemic stroke, rituximab

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INTRODUCTION

Intravascular lymphomatosis (IVL) is a rare high-grade subtype of extranodal non-Hodgkin lymphoma with a tendency to invade small vessels^(1,2), especially those in the skin, the central nervous system and the endocrine gland⁽³⁾. It usually goes undiagnosed until the time of

autopsy because of its protean neurological manifestations. From literature review, only one patient who presented with focal neurological signs and was diagnosed post mortem as having IVL has been reported in Taiwan⁽⁴⁾. We herein report two patients with multiple recurrent strokes for whom the diagnosis was made ante mortem through brain biopsy.

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CASE REPORT

Case 1

A 70-year-old woman was admitted because of acute onset of dressing apraxia. She had long-term hypertension and hyperlipidemia. Eight weeks previously, she had suffered from mild aphasia, visual impairment with right hemianopsia, acalculia, and memory impairment. The brain magnetic resonance imaging (MRI) showed lesions in the left parieto-occipital region (Fig. 1A), which were hyperintense on diffusion weighted imaging (DWI) and hypointense on apparent diffusion coefficient (ADC) maps. She was treated with aspirin for suspected ischemic stroke at another hospital. Two weeks prior to hospital arrival, she was found to have difficulty in dressing and a tendency to neglect her left limbs. She did not have

symptoms of respiratory or gastrointestinal infection or receive vaccination in the past 2 months. On admission, she was disoriented to place and had impaired immediate and recent memory. Other significant neurological findings included sensory aphasia, left hemianopsia, and a Gerstmann's syndrome. Her muscle strength was normal initially. Electrocardiography showed normal sinus rhythm without atrial fibrillation and transthoracic echocardiography was unremarkable. MRI showed multiple bilateral ischemic lesions (Fig. 1B), of which some were hyperintense on DWI and hypointense on ADC maps, with minimal hemorrhagic transformation. Magnetic resonance angiography (MRA) revealed mild stenosis of the bilateral internal carotid arteries, middle cerebral arteries, anterior cerebral arteries and the left vertebral artery. She was treated with aspirin 100 mg per

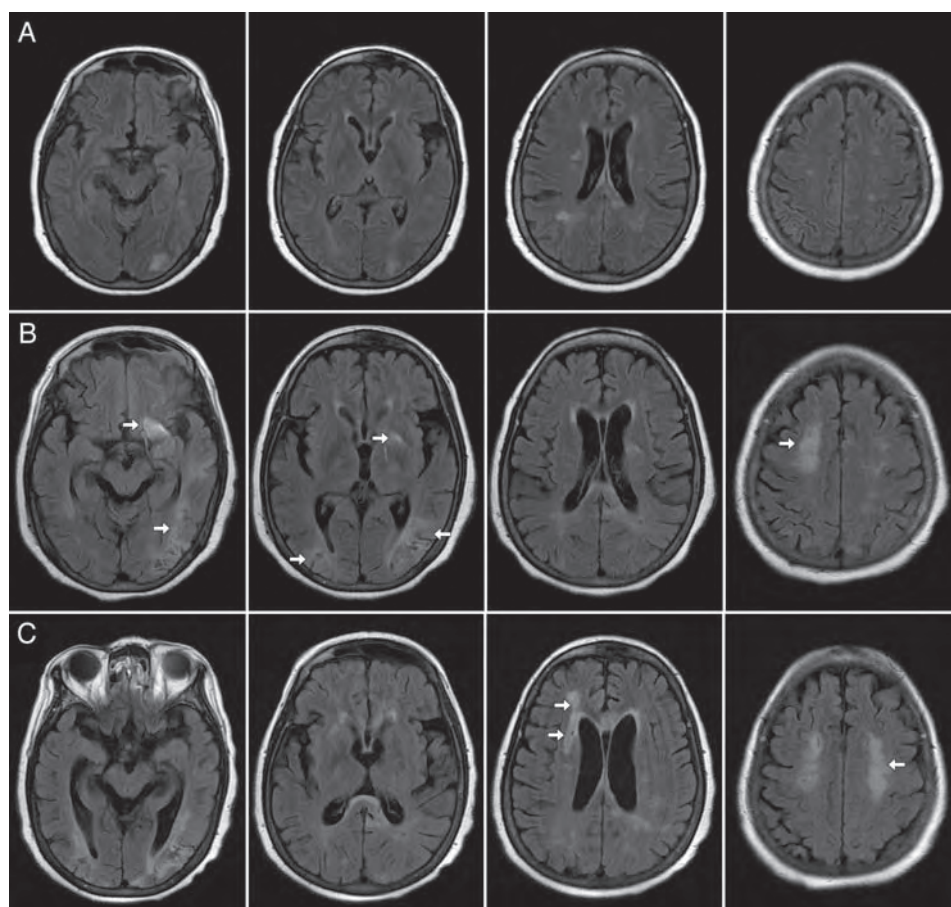


Figure 1. T2 FLAIR axial brain MRI shows progression of cerebral infarcts: at onset (A), 8 weeks after onset (B), and 13 weeks after onset (C). Arrows indicate new lesions as compared to the images above the current row.

day and was discharged in stable condition.

Five weeks later, she was admitted again because of acute drowsiness and global aphasia. She also had conjugate deviation of eyes to the left side and right hemiparesis. Muscle power was graded as 3 on the right side and as 4 on the left side. MRI showed multiple multistage infarctions (Fig. 1C) and minimal hemorrhage in bilateral cerebral hemispheres. MRA revealed mild stenosis of the bilateral internal carotid arteries, middle cerebral arteries, anterior cerebral arteries and the left vertebral artery. Cerebral angiography of bilateral carotid arteries (Fig. 2) revealed a mildly irregular contour of the intracranial vessels, including the anterior cerebral arteries and the middle cerebral arteries, with several focal segmental narrowings that resemble cerebral vasculitis. We arranged laboratory tests including serum complement component 3 and 4, thyroid stimulating hormone, free thyroxine, homocysteine, tumor markers (squamous cell carcinoma antigen, alpha-fetoprotein, carcinoembryonic antigen, carbohydrate antigen 125), serologic tests for syphilis, and anticardiolipin antibodies to survey unusual etiologies of strokes. The laboratory results

were unremarkable except for an abnormal antinuclear antibody (ANA) titer (1:160) and an increased erythrocyte sedimentation rate (88 mm/hr). Cerebrospinal fluid (CSF) study revealed neither evidence of pleocytosis nor glucose consumption, but an elevated CSF total protein level (152 mg/dL, normal: 15-45 mg/dL) and an elevated CSF IgG level (24.8 mg/dL, normal: 0.48-5.86 mg/dL). Immunofixation electrophoresis of CSF revealed a monoclonal gammopathy of IgG with lambda light chains. For further investigation of the cause of stepwise recurrent strokes with bilateral cerebral infarcts and the appearance of cerebral vasculitis on angiography, we performed brain biopsy of the right frontal subcortical region. The histopathology revealed enlarged discohesive cells with high nucleus-to-cytoplasm ratio lodged in the vascular spaces of the brain parenchyma and the leptomeninges (Fig. 3A). These atypical cells were immunoreactive for anti-CD45 and anti-CD20 antibodies (Fig. 3B). The pathological findings met the diagnosis of intravascular large B-cell lymphoma (IVLBCL) or IVL. However, chemotherapy was not given owing to poor performance status of the patient. She died of septic shock one month after the pathological diagnosis was made.



Figure 2. Cerebral angiography of the left common carotid artery revealed several focal segmental irregular narrowings (arrows).

Case 2

A 65-year-old woman presented to the emergency department with sudden onset of consciousness disturbance. Her medical history included colon cancer (adenocarcinoma) post operation, right breast cancer (ductal carcinoma in situ) post operation, type 2 diabetes mellitus and hypertension under medical control. At 20 minutes after arrival at our hospital, she was stuporous, and displayed conjugate deviation of eyes to the right side, left central facial palsy, left hemiparesis (muscle power graded as 5 on the right side and as 3 on the left side). Brain CT was unremarkable and the initial National Institutes of Health Stroke Scale score was 17. She received 45 mg (0.6 mg/kg) of intravenous recombinant tissue plasminogen activator 85 minutes after the onset of symptoms. After treatment, the aforementioned neurological deficits were much improved. Brain MRI at 24 hours showed a right frontal infarct (Fig. 4A), which was hyperintense on DWI and showed restricted diffusion on ADC maps. MRA of intracranial arteries was unremarkable. Five days later, she was discharged with clear consciousness, normal muscle

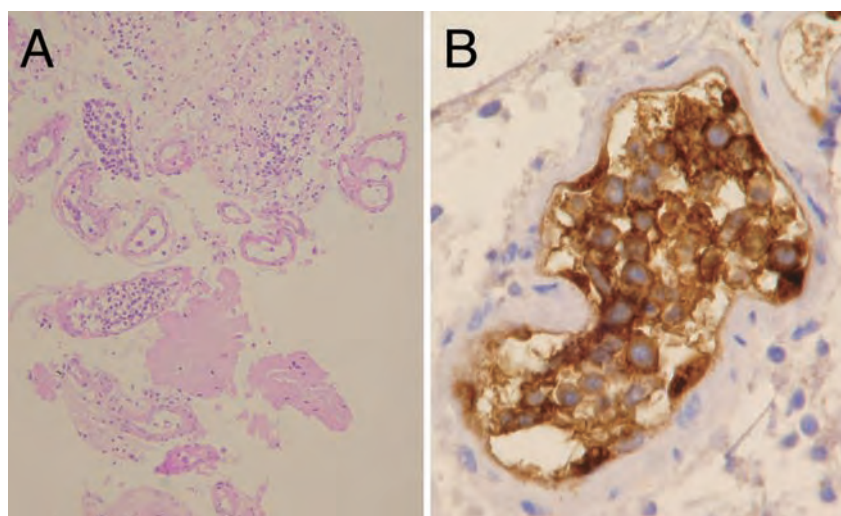


Figure 3. The histopathology revealed enlarged atypical large cells in the vascular spaces (A) (hematoxylin-eosin, original magnification $\times 100$). These atypical cells were immunoreactive for anti-CD20 antibody (B) (diaminobenzidine as chromogen, original magnification $\times 400$).

strength of all four limbs, and she could walk with slight assistance.

Three weeks after the first admission, another episode of acute slurred speech, right-sided weakness, and easy choking developed. Brain MRI showed progression of lesion size in the right frontal area (Fig. 4B). In addition, there were new hyperintense lesions on DWI in bilateral cerebral hemispheres. MRA did not find stenosis of intracranial arteries. During the hospital stay in another hospital, she experienced gradual deterioration of consciousness even after treatment with intravenous piperacillin and tazobactam for *Pseudomonas aeruginosa* urinary tract infection.

Five weeks after the first admission, a third episode of acute neurological deficits consisting of acute slurred speech and left-sided weakness developed. At this point she was referred to our hospital. On admission, she was clear, but had mild motor and sensory aphasia, right hemianopia, left central facial palsy, and bilateral hemiparesis (muscle power graded as 3 in the right limbs, as 3 in the left upper limb and as 2 in the left lower limb). Electrocardiography showed normal sinus rhythm without atrial fibrillation. Brain MRI revealed multiple hyperintense lesions on DWI in bilateral cerebral hemispheres. These lesions showed restricted diffusion on ADC maps, indicating acute cerebral infarcts. After contrast administration, no enhancement

was observed. We performed brain biopsy of the right frontal subcortical region. The histopathology showed enlarged discohesive atypical cells, with a high nucleus-to-cytoplasm ratio, mainly lodged in the vascular spaces of the brain parenchyma and the leptomeninges (Fig. 5A). Immunohistochemically, these atypical cells are strongly positive for CD20 (Fig. 5B), positive for MUM-1 and bcl-6, and negative for CD3, CD5, CD10, CD138, TdT, and cytokeratin (AE1/AE3). The pathological findings met the diagnosis of IVL or IVLBCL. She underwent whole brain radiotherapy with a total dose of 45 gray. Biotherapy and chemotherapy with R-COP regimen (including rituximab, an antibody against the protein CD20, plus cyclophosphamide, vincristine, and prednisone) was firstly administered 8 days after the radiotherapy (10 weeks after the onset). After 6 courses of biotherapy and chemotherapy at an interval of 3 weeks, her muscle strength (graded as 4 in the right limbs, as 3 in the left upper limb and as 2 in the left lower limb), dysarthria and aphasia were partially improved. The follow-up brain MRI before the 6th course of biotherapy and chemotherapy (25 weeks after the onset) showed partial resolution of the cerebral infarcts (Fig. 4D). After contrast, there was no enhancement of the lesions. The disease process seemed to have stopped until 8 months after the onset. Then she started to deteriorate in consciousness and she became stuporous at 10 months after the onset.

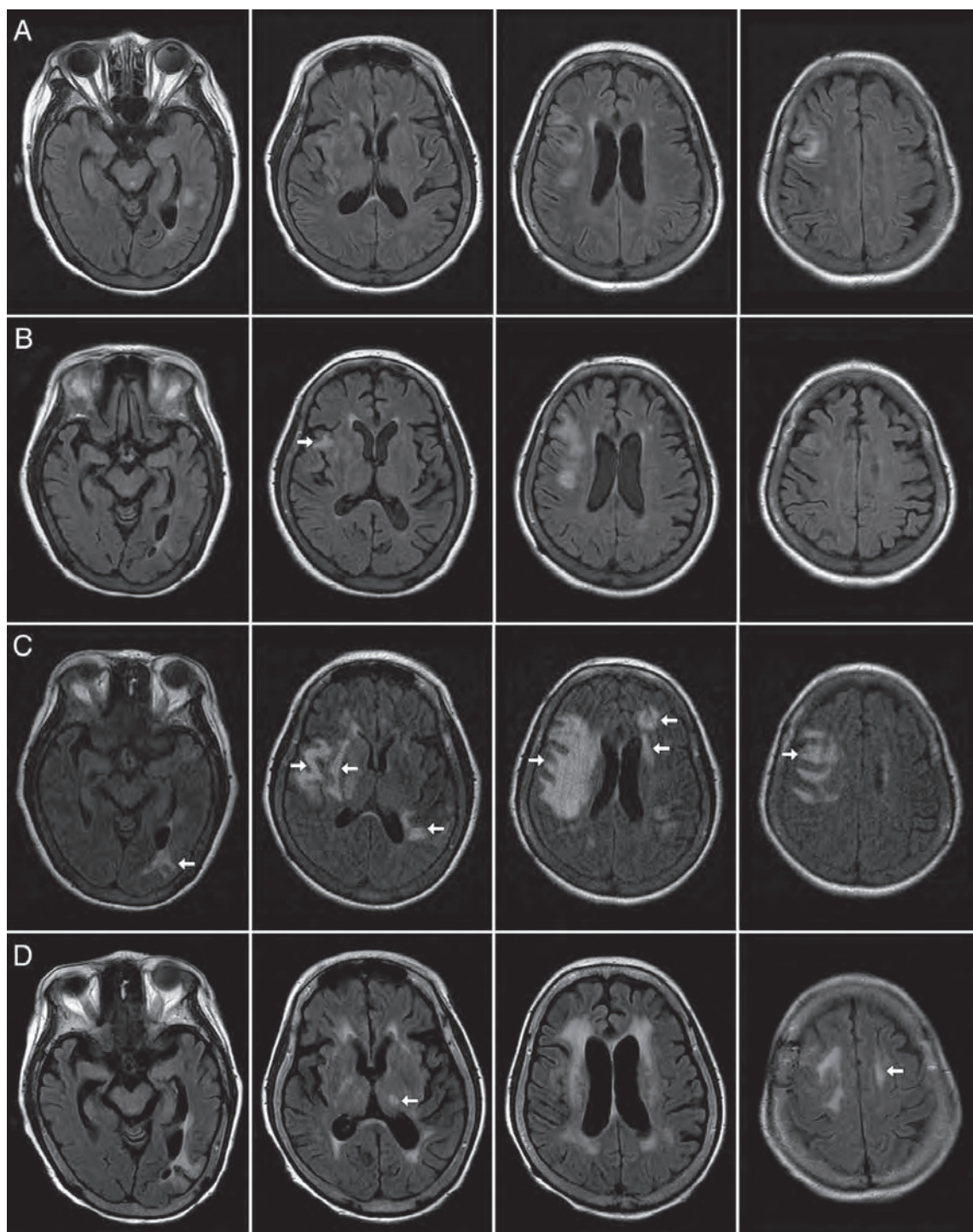


Figure 4. T2 FLAIR axial brain MRI shows evolution of cerebral infarcts: at onset (A), 3 weeks after onset (B), 5 weeks after onset (C), and resolution of cerebral infarcts at 25 weeks after onset when the patient has received five courses of rituximab-containing chemotherapy (D). Arrows indicate new lesions as compared to the images above the current row.

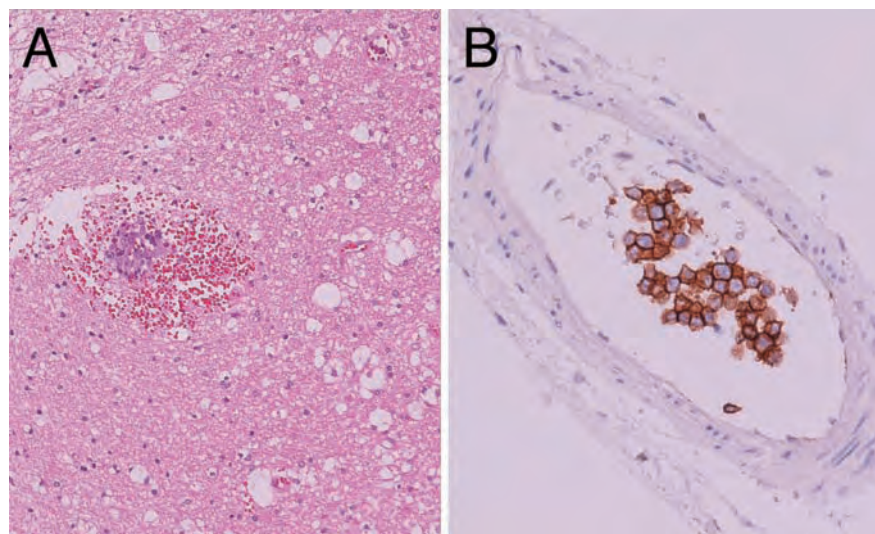


Figure 5. The histopathology showed enlarged atypical large cells in the vascular spaces (A) (hematoxylin-eosin, original magnification $\times 100$). These atypical cells were immunoreactive for anti-CD20 antibody (B) (diaminobenzidine as chromogen, original magnification $\times 200$).

DISCUSSION

The common differential diagnoses of rapidly recurrent multiple stroke-like episodes include embolism of cardiac origin, demyelination diseases such as multiple sclerosis or acute disseminating encephalomyelitis, cerebral venous thrombosis, paraneoplastic syndromes, thyroid disorders, vasculitis, infection, or neoplasm. The present two cases did not have atrial fibrillation, valvular heart disease, or other cardiac disorders predisposing to cardioembolic stroke. Demyelination diseases were not likely for either patient considering their old age, lack of history of recent infection or vaccination, and absence of typical chronic course of disease progression.

In these two cases, cerebral venous thrombosis could not be completely excluded without a magnetic resonance venography. Paraneoplastic syndromes and thyroid disorders were ruled out by the unremarkable tumor markers and thyroid function tests in the first case. Primary central nervous system (CNS) lymphoma should also be considered in such cases with recurrent stroke-like episodes and progressive lesions in the bilateral cerebral subcortical regions. Although the lesions observed were relatively non-heterogeneous, gliomatosis cerebri, astrocytoma or even glioblastoma multiforme should still be taken into account before tissue proof.

In the first case, findings on cerebral angiography

were consistent with a diagnosis of vasculitis. In spite of ANA positivity, vasculitis secondary to autoimmune disorders was unlikely without the presence of classic systemic manifestations. Hence, primary CNS vasculitis was suspected. Nevertheless, IVL may have characteristics of CNS vasculitis on cerebral angiography⁽⁵⁾.

In a series of 38 Western cases of IVL, the most common presenting manifestations were systemic symptoms (56%), i.e., fever, weight loss, and night sweats, followed by cutaneous lesions (39%) and neurological symptoms (34%)⁽⁶⁾. The most commonly involved organs included the skin (39%), the central nervous system (39%) and the bone marrow (32%)⁽⁶⁾. A total of 13 Taiwanese cases of pathology-proven IVL have been reported in 6 references^(4,7-11). Eight of them presented with fever rather than neurological symptoms. Only one patient had focal neurological symptoms as the initial manifestations⁽⁴⁾. This 49-year-old woman experienced rapidly progressive left limb weakness. She was treated with pulse steroid and intravenous immunoglobulin for a presumed demyelination disorder. She died 3 months later and was finally diagnosed as having IVL involving the brain, the spinal cord, the heart, the lungs, the kidneys, the adrenal glands, and the skin at autopsy⁽⁴⁾.

Rapidly progressive encephalopathy due to stroke-like syndromes and multifocal neurological signs including focal neurological deficits, encephalopathy, and seizure

are common neurological manifestations of IVL⁽¹²⁾. The possibility of IVL should be considered in adult patients with rapidly recurrent stroke-like syndromes (as rare as one in every 5,000 cases of recurrent multifocal cerebral infarcts⁽¹³⁾, vascular dementia with stepwise downhill patterns^(1,6) and appearance of vasculitis on angiography⁽⁵⁾. Neuroimaging findings of IVL can range from infarct-like lesions to diffuse involvement of the deep white matter. Linear, punctate, and patchy enhancement on contrast MRI has been reported to suggest a diagnosis of IVL⁽¹⁴⁾. Random skin biopsy of apparently healthy skin may be first considered in patients with suspected IVL⁽²⁾. Pathological examination of brain biopsy is required for definitive diagnosis.

In spite of poor prognosis, initiation of combination chemotherapy should be considered^(1,2,6,15). The commonly used regimen consisted of cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone with or without rituximab. Rituximab is a monoclonal antibody against CD20 that is effective against CD20-positive B-cell lymphomas⁽¹⁶⁾. In a retrospective analysis of IVL in 106 patients in Japan⁽¹⁶⁾, patients in the treatment group with rituximab showed improved clinical outcomes as compared with those without rituximab. The progression-free survival (PFS), which indicated duration from the date of diagnosis to the first day of disease progression, relapse, or death, and the overall survival (OS) at 2 years after diagnosis were significantly higher for patients in the rituximab-containing chemotherapy group than for those without rituximab treatment (PFS, 56% versus 27%, $P=0.01$; OS, 66% versus 46%, $P=0.01$). Although the worldwide experience of autologous stem-cell transplantation for IVL is limited, it might be considered as the second line treatment of relapsing IVL⁽¹⁷⁾.

CONCLUSION

IVL can present as recurrent and stepwise strokes in a short time of period. Rituximab-containing chemotherapy may be considered for IVL despite its poor prognosis.

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