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Status Epilepticus as the Initial Presentation of Intravascular Lymphoma

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Key Words

Status epilepticus · Intravascular lymphoma · Diffusion-weighted imaging

Abstract

Intravascular lymphoma (IVL) is a rare disease form of malignant lymphoma, and it is characterised by the selective growth of lymphoma cells within the lumina of vessels. Identification of this disease at an early stage is difficult because of non-specific clinical symptoms and neuroradiological findings. Most reported IVL cases are diagnosed at post-mortem following autopsy. We report the case of a patient who presented with status epilepticus (SE) as the initial manifestation of IVL. Despite the administration of anti-convulsant agents and general care the patient's condition deteriorated rapidly after admission, culminating in death due to respiratory failure and heart failure 21 days after the onset of symptoms. Post-mortem examination revealed IVL in the brain and multiple organs. Epileptic seizures often appear during the clinical course of IVL; however, they occur most frequently at advanced stages. Diagnosis of IVL that first presents with SE is of clinical importance because the treatment and prognosis of acute SE arising from IVL are different from those of SE originating from other causes.

Introduction

Intravascular lymphoma (IVL) is a rare disease form of malignant lymphoma, and it is characterised by the selective growth of lymphoma cells within the lumina of vessels. Identification of this disease at an early stage is difficult because of its non-specific clinical symptoms and neuroradiological findings [1]. Most reported IVL cases have been diagnosed at post-mortem following autopsy. Survival time is less than 1 year in most patients (mean, 5 months) [2].

We report the case of a patient with IVL who first presented with status epilepticus (SE). His condition followed a fulminant course, culminating in death 21 days after the onset of symptoms. The radiological and pathological characteristics of the patient's brain lesions and the mechanism of seizures are also discussed here.

Case Report

A 76-year-old man with pulmonary emphysema was admitted to our institution following acute onset of convulsions. Several hours before seizure onset, he was asymptomatic and was able to drive his motorbike independently. On physical examination, the patient's temperature was 35.0°C, and no skin lesions were observed. He was comatose, his pupils were isocoric, and persistent clonic seizures of the head were observed. His peripheral white blood cell count and haemoglobin level were 13,400/ μ l and 14.1 g/dl, respectively. Blood chemistry results were as follows: aspartate aminotransferase, 41 IU/l; alanine aminotransferase, 14 IU/l and serum C-reactive protein, 0.5 mg/dl. Lactate dehydrogenase was elevated to 515 IU/l. Serum albumin, blood sugar and sodium levels were 3.4 g/dl, 94 mg/dl, and 133 mmol/l, respectively. Cerebrospinal fluid analysis showed 3 white blood cells/ mm^3 and a protein level of 57 mg/dl; no bacteria or malignant cells were found. Brain computed tomography revealed only mild cortical atrophy. The patient was diagnosed with SE and was administered immediate treatment with intravenous phenytoin followed by repeated intravenous administrations of diazepam. The seizures were not controlled by phenytoin; however, they ceased after continuous administration of intravenous midazolam. Brain diffusion-weighted imaging (DWI) performed on admission showed a hyperintense lesion in the right fronto-temporal cortex ([fig. 1](#)). This lesion was almost completely restricted to the cortex and did not comprise a single vascular territory. Additional magnetic resonance imaging (MRI) sequences such as T2-weighted imaging were not performed because his condition was critical.

In addition to continuous midazolam infusion, valproic acid and carbamazepine were administered through nasogastric tubes from the time of admission. The patient was intubated the day after admission, and he subsequently developed pneumonia that was treated with antibiotics. His condition was further complicated by inappropriate secretion of antidiuretic hormone. Electroencephalography performed 3 days after admission under continuous midazolam administration showed diffuse dysrhythmic theta-delta activity without epileptic discharge. The patient's respiratory condition deteriorated, and he was put on a respirator 9 days after admission. Hypoalbuminaemia ensued, and he was administered total parenteral nutrition. Despite treatment with anti-epileptics, antibiotics and simultaneous general care, the patient's condition deteriorated further. Rapid progression of respiratory failure followed, and he died 21 days after the onset of symptoms.

Autopsy findings suggested that the patient died from respiratory failure and heart failure resulting from acute purulent pericarditis. Microscopic examination revealed large malignant lymphoma cells in the small blood vessels of the brain, heart, liver, prostate, adrenal gland and bladder. These abnormal lymphoid infiltrates were entirely intravascular and positive for B-cell antigen CD20 but negative for CD3, CD5, CD10 and bcl-2 ([fig. 2](#)). Similar lymphoid infiltrations were observed predominantly in the cortex in the bilateral frontal, parietal, temporal and occipital lobes, and most significantly, in the right frontal lobe of the brain. Lymphoma cells were also observed in the vessels of the subarachnoid space. The cerebral tissue at the frontal area showed some petechial haemorrhages around the capillaries, and this tissue was characterized by the presence of neuronal changes and mild spongiosis, absence of neuronal ferrugination, coagulative necrosis, chronic inflammation, macrophages, hemosiderin pigmentation, neo-vascularization and cavitation. These findings suggested a phase of acute cerebral injury secondary to vessel occlusion. The final diagnosis was IVL.

Discussion

We report the clinical course of a patient who developed acute SE as the first manifestation of IVL in the absence of other symptoms. Although IVL generally presents as a subacute progressive disease, this case was characterized by the presence of intractable SE from its initial presentation. It followed a fulminant and rapidly progressive course that resulted in death of the patient 21 days after onset. The diagnosis of IVL was confirmed by autopsy.

IVL is characterized by a variety of symptoms resulting from occlusion of small vessels by tumour cells in different organ systems, especially the nervous systems. A previous study suggested that all patients with IVL have one or more of four presentations: progressive, multifocal cerebrovascular events; spinal cord and nerve root vascular syndrome; subacute encephalopathy and peripheral or cranial neuropathies [3]. Common to all these presentations are multiple areas of capillary, arteriole and venule occlusion. Regarding the occurrence of seizures associated with IVL, epileptic seizures have been reported in 8.8–25% patients with IVL [4–6]. Epileptic seizures in patients with IVL reportedly occur at a more advanced stage in most cases [6, 7]; however, patients suffering from epileptic seizures at IVL onset have also been reported [4, 6, 8, 9]. Case reports and literature reviews have shown that epileptic seizures as the first manifestation of IVL are found in 3–4% patients with IVL [4, 6]. However, IVL initially presenting as SE has rarely been reported. This case highlights the importance of making an accurate diagnosis of IVL in patients who initially present with SE.

Post-mortem examination of the patient revealed a phase of acute neural injury, which may have occurred 1–2 days after an acute infarction [10]. Petechial haemorrhages around capillaries were also noted. Most previous reports of patients with IVL accompanied by epileptic seizures have documented the presence of radiologically detectable infarct lesions at the onset of epilepsy or ischemic necrosis at autopsy; however, some IVL cases with epilepsy have shown no infarcted regions at autopsy. Although this case showed SE as the first manifestation of IVL, autopsy at 21 days after SE onset revealed acute-phase lesions that had probably occurred 1–2 days after acute infarction; however, there were no chronic or subacute lesions, suggesting that infarctions did not occur at SE onset. Moreover, DWI suggested no infarcted lesion at SE onset because the lesion seen on DWI did not comprise a single vascular territory. Both DWI and autopsy findings were suggestive of a pathogenesis different from that of post-stroke seizures. Although the mechanism of seizures associated with stroke is not completely understood, metabolic changes, acute glutamate release, changes in the penumbra zone and anoxic depolarization may provoke early seizures [11]. In this case, hypoperfusion due to small vessel stenosis by IVL cells, small petechial haemorrhages from capillaries, meningeal involvement of IVL cells or metabolic effects are possible explanations for the mechanism underlying SE due to IVL.

DWI has proved to be a useful tool for the diagnosis of acute ischemia caused by IVL. A previous study has revealed that DWI changes in IVL possibly reflect both IVL-associated ischemia and the movement of tumour cells through the vessel wall to the cerebral white matter [12]. A dynamic pattern of MRI lesions with resolution of some DWI lesions may indicate the diagnosis of IVL through neuroimaging. In this case,

the patient's critical condition did not allow serial DWI studies; therefore, IVL was not considered.

In conclusion, SE can present as the initial manifestation of IVL and should be included in the differential diagnosis for etiologically undiagnosed SE in elderly patients. IVL recognition is of clinical importance because the treatment and prognosis of acute SE resulting from IVL are different from those of SE with different origins. Early detection, aggressive attempts at early diagnosis and appropriate treatment may prove beneficial to these patients.

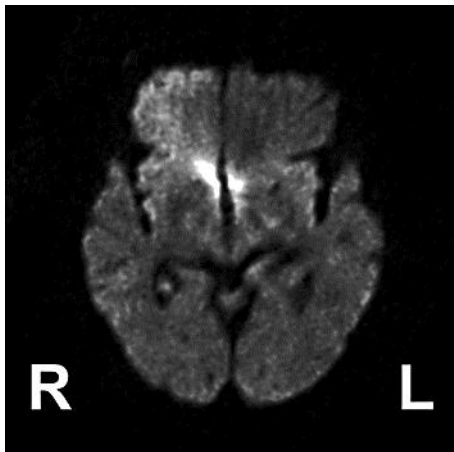


Fig. 1. Diffusion-weighted MRI performed on the day of onset reveals a high-signal intensity lesion in the right fronto-temporal cortex.

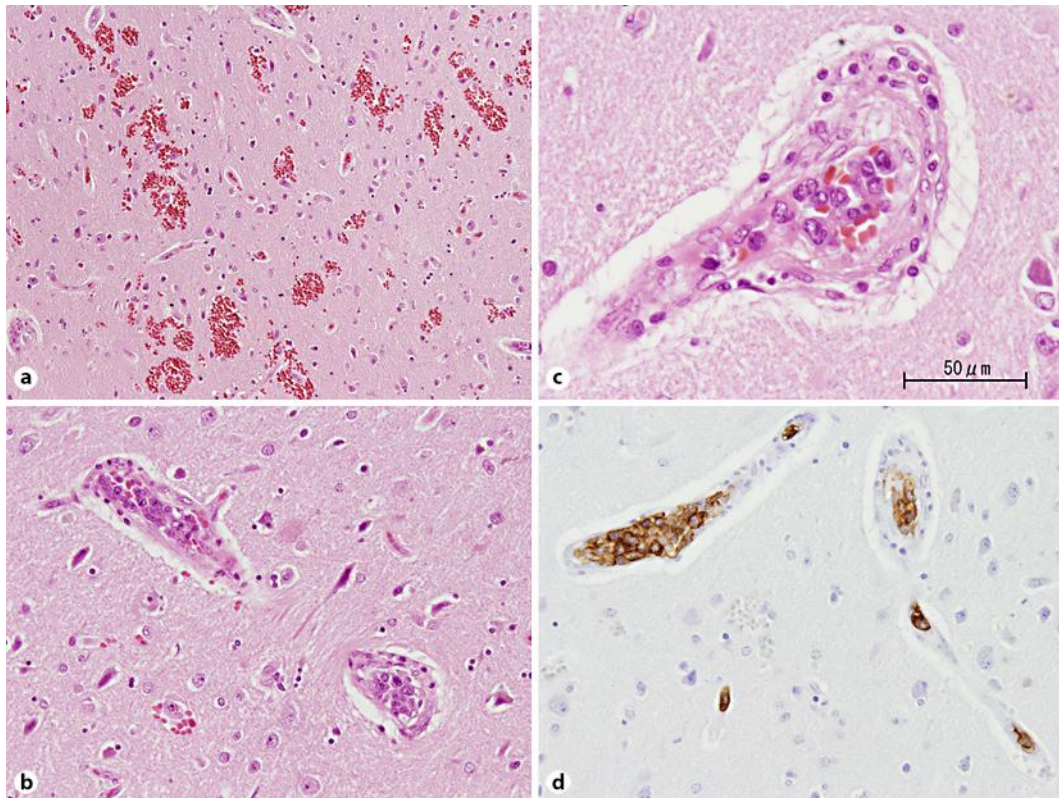


Fig. 2. Photomicrographs of autopsy specimens. **a** The cerebral tissue at the frontal area shows some petechial haemorrhages around the capillaries, and this tissue is characterized by the presence of neuronal changes and mild spongiosis (H&E, $\times 10$). **b** Cerebral tissue from the frontal area (H&E) shows small blood vessels that are filled with malignant lymphoma cells ($\times 20$). **c** Large lymphoma cells filling a small blood vessel in the frontal area, as seen by H&E staining at a higher magnification with a scale bar ($\times 40$). **d** Immunostaining of the cerebral tissue with a CD20 monoclonal antibody reveals strong immunoreactivity in the tumour cells occupying the small vessels ($\times 20$).

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