

Case report

# Rapid deterioration of intravascular large B-cell lymphoma with mass formation in the trigeminal nerve and multiple organ infiltration: An autopsy case report

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Intravascular large B-cell lymphoma (IVLBCL) is a rare lymphoma characterized by the selective growth of lymphoma cells within the lumen of vessels. We describe the case of a 69-year-old male who presented with marked pain in the left facial region. Gadolinium-enhanced magnetic resonance imaging revealed a swollen left trigeminal nerve (TN) and positron emission tomography/computed tomography demonstrated fluorodeoxyglucose-only uptake at the same site. The patient had high serum lactate dehydrogenase and soluble interleukin-2 receptor levels. As random skin biopsy and bone marrow biopsy detected no abnormal pathogenesis, open biopsy of the TN was performed, revealing diffuse large B-cell lymphoma (DLBCL). However, ground glass opacities rapidly developed in both lung fields with severe respiratory failure. The patient died of progressive disease before the initiation of chemotherapy. Postmortem examination revealed widespread lymphoma cells in the lumen of vessels in multiple organs, including the lungs, excluding the bone marrow and skin. Lymphoma cells formed a mass in the TN and left lumbar plexus. A diagnosis of IVLBCL was made based on the postmortem pathological analysis. DLBCL of abnormal sites, such as the peripheral nervous system, should be considered in cases of IVLBCL as a differential diagnosis.

**Keywords:** Intravascular large B-cell lymphoma, trigeminal nerve, random skin biopsy, bone marrow biopsy, biopsy

## INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is characterized by lymphoma cell invasion in the lumen of vessels, particularly in capillaries.<sup>1</sup> IVLBCL widely disseminates to extranodal sites, including the skin and bone marrow (BM).<sup>2,3</sup> Among the many clinical presentations of IVLBCL, B symptoms are a common manifestation, occurring in 54–76% of patients.<sup>4–6</sup> Although the prognosis of IVLBCL is poor due to the frequent delay in early diagnosis, random skin biopsy (RSB) and BM biopsy (BMB) have improved the accuracy of diagnosis, resulting in the prompt initiation of chemotherapy and improved outcomes.<sup>1,3,5,6</sup> However, the results, including flow cytometry and pathological findings of these samples, are often unhelpful in making a diagnosis.

We present the case of a patient with IVLBCL resulting in mass formation in the trigeminal nerve (TN). This case

had concurrent abnormal clinical manifestations, such as failure to detect IVLBCL by RSB and BMB, resulting in death due to rapid deterioration. Autopsy revealed unique IVLBCL invasion of the TN, left lumbar plexus, and lumen of vessels of multiple organs, excluding the skin and BM.

## CASE REPORT

A 69-year-old man was transferred to our hospital because of progressive headache and numbness in his left face for a month. Although an anti-inflammatory analgesic was administered, pain and B symptoms, such as fever and unintentional weight loss of 16% over 6 months, were not relieved. Neither the patient nor his family had a remarkable medical history. Physical examination, including neurological examination, revealed no abnormalities, though he had severe allodynia in the left side of his face.


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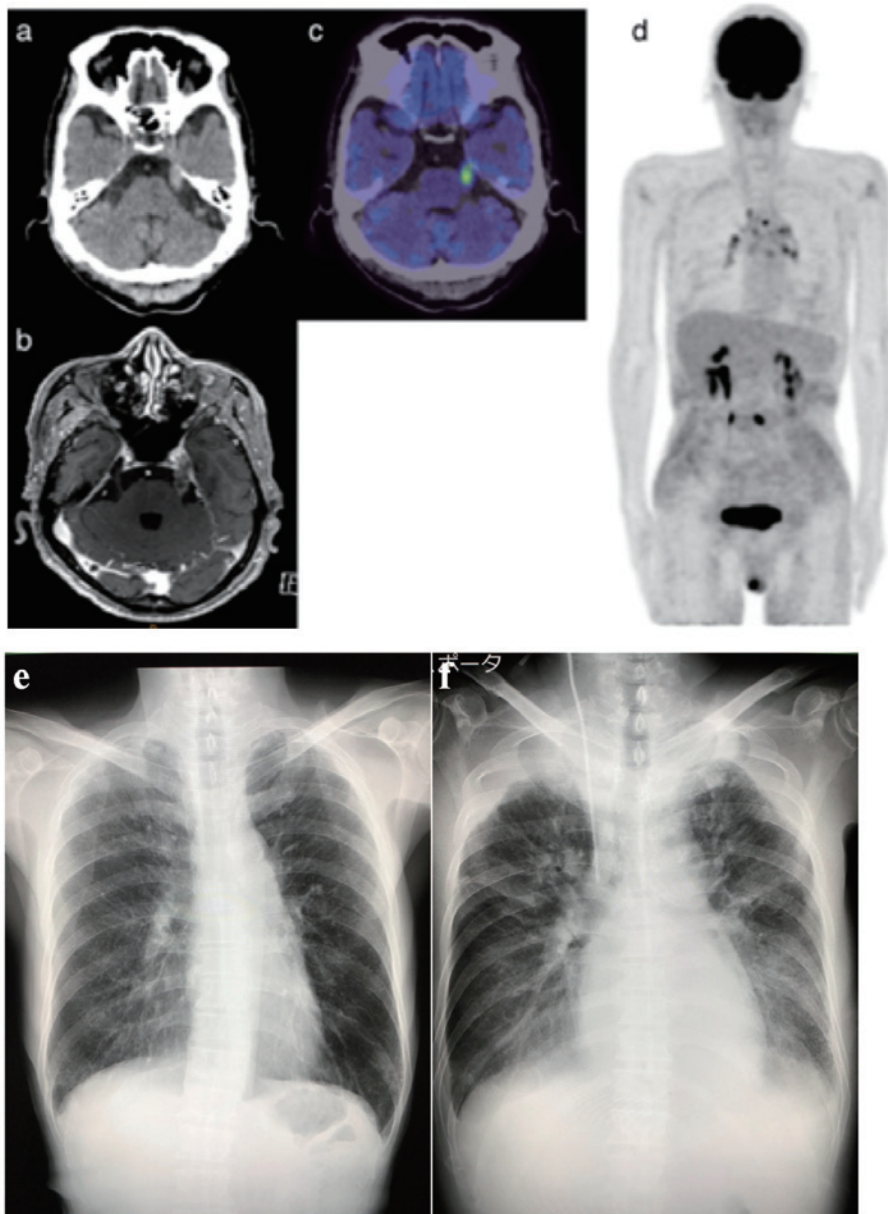
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Laboratory findings included anemia (Hb 11.3 g/dL), and high lactate dehydrogenase (LDH, 571 U/L), aspartate aminotransferase (AST, 88 U/L), alanine aminotransferase (ALT, 64 U/L), and soluble interleukin-2 receptor (sIL-2R, 3970 IU/mL) serum levels. Other tumor markers, such as carcinoembryonic antigen, were not increased. The patient was serologically negative for viruses, including EBV, cytomegalovirus, HTLV-1, hepatitis B virus and hepatitis C virus. Left TN swelling measuring 15 mm was observed on enhanced computed tomography (CT) and magnetic resonance imaging; isotope uptake was noted in the same region on positron

emission PET-CT (Figure 1).

To obtain a definite pathological diagnosis, open tumor biopsy of the mass in the TN was performed. In the early postoperative period, the patient developed hypoxemia, which presented as a frosted glassy shadow in both lungs on chest radiography (Figure 1). Although aggressive chemotherapy was initiated after recovery from surgery, progressive lung manifestations were uncontrollable. Oxygen and prednisolone at a daily dose of 60 mg were administered, but the patient died 7 days after the operation because of progressive respiratory failure.



**Fig. 1.** Imaging examination on admission. Enhanced computed tomography (CT) (a) and gadolinium-enhanced T1-weighted image (b) showing swelling of the left trigeminal nerve. <sup>18</sup>F-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET)-CT (c-d) showing marked FDG uptake in the left trigeminal nerve, although there are no other FDG uptake areas. Comparison between chest radiography on admission (e) and post-biopsy (f). Ground glass opacities rapidly developed in both lung fields.

## PATHOLOGICAL FINDINGS

BM biopsy, including flow cytometry, RSB, and cerebrospinal fluid cytology, provided no neoplastic evidence. Open tumor biopsy of the mass in the TN demonstrated the formation of nodular lesions by atypical large lymphoid cells within the endoneurium of the TN. These cells were immunohistochemically positive for CD20, BCL6, and IRF4/MUM-1, and negative for CD3, CD5, and CD10. A diagnosis of diffuse large B-cell lymphoma, NOS, non-GCB type was thus made (Figure 2).

Autopsy revealed infiltration of lymphoma cells in the endoneurium of the TN (Figure 3), left nerve root of the fifth lumbar vertebra, and lumen of vessels of the lungs, cerebellar peduncle, pituitary gland, and adipose tissues of kidney, pancreas, adrenal gland, and gallbladder. A diagnosis of IVLBCL with mass formation in the TN was made (Figure 4).

## DISCUSSION

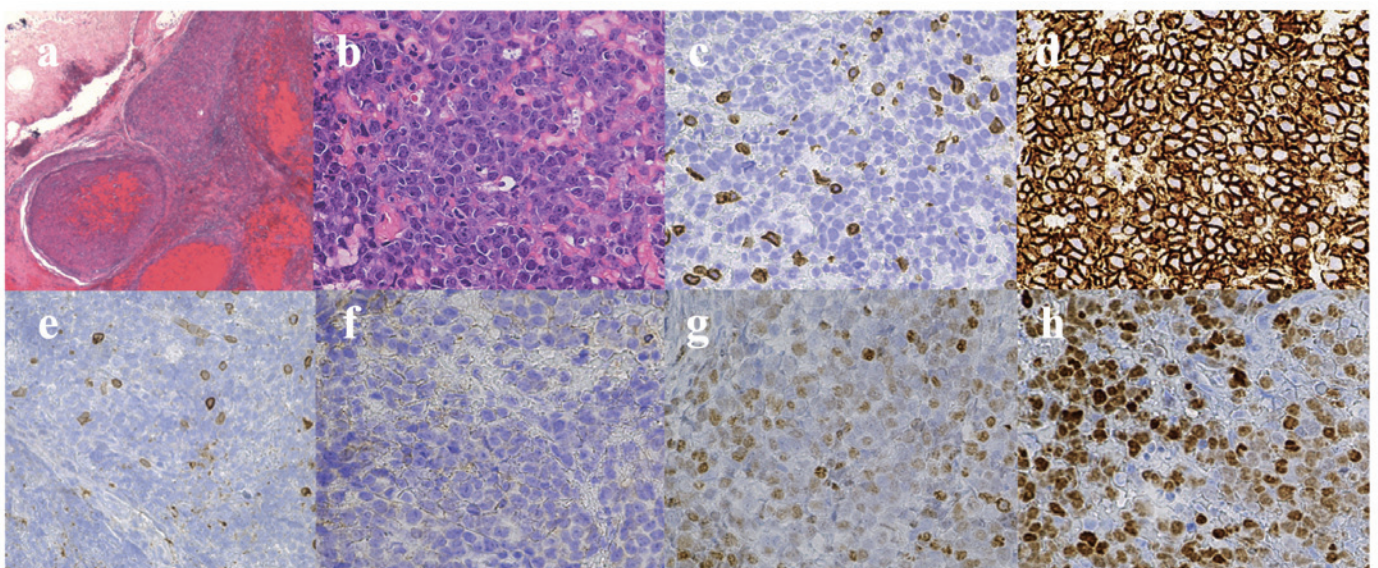
Although IVLBCL develops in the vessels of multiple organs, such as the skin, lungs, and BM, our case had three unique clinical manifestations. The first was the mass in the peripheral nerves as the primary site. The second was the absence of invasive lesions in the BM and skin. The third was rapid respiratory failure progression resulting in death before the administration of chemotherapy.

Regarding the first point, although IVLBCL usually presents with intravascular invasion, it occasionally infiltrates extra-vascular sites. Matsue *et al.* reported on neurolymphomatosis among patients with IVLBCL and proposed that this manifestation is a distinctive subtype of IVLBCL.<sup>7</sup> In their report, neurolymphomatosis developed in commonly invaded

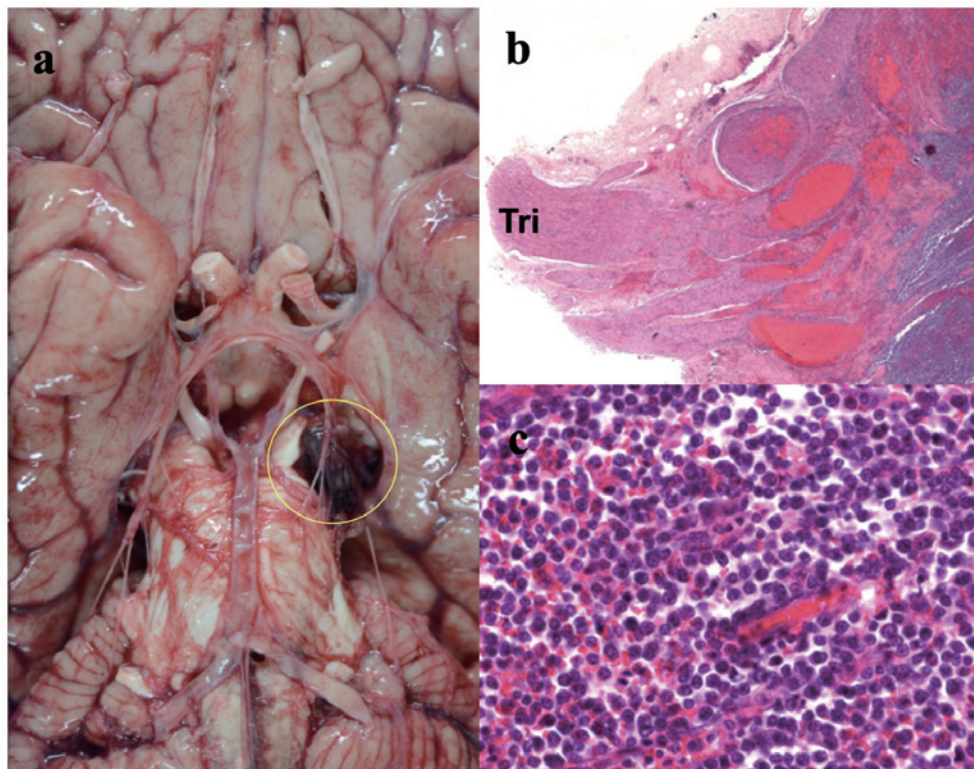
sites, such as the BM and skin, in the relapse phase in four patients. Although our patient had masses in the TN, a peripheral nerve (PN), and an extra-vascular location, this is the first case in which the mass in a PN was detected as the primary site of invasion without other infiltrative sites. Neurolymphomatosis of DLBCL was reported to exhibit lymphomatous infiltration, especially in the endoneurium,<sup>8</sup> and Yamada *et al.* reported neurolymphomatosis coexisting with IVLBCL and DLBCL.<sup>9</sup> Similarly, our case demonstrated the infiltration of lymphoma cells into the endoneurium of TN and lumbar vertebra. As approximately one-half neurolymphomatosis cases of DLBCL had widespread systemic lymphoma at the time of autopsy,<sup>8</sup> IVLBCL may be a specific feature of DLBCL rather than a distinct disease entity of DLBCL.

In terms of the site of invasion of IVLBCL, the central nervous system (CNS) is the most common site. Although a recent investigation revealed the relationship between CNS invasion and the expression of PD-L1,<sup>10</sup> our case was negative for PD-L1 in both the TN and lung lesions. The PN invasion mechanism of IVLBCL may be different from that of CNS invasion.

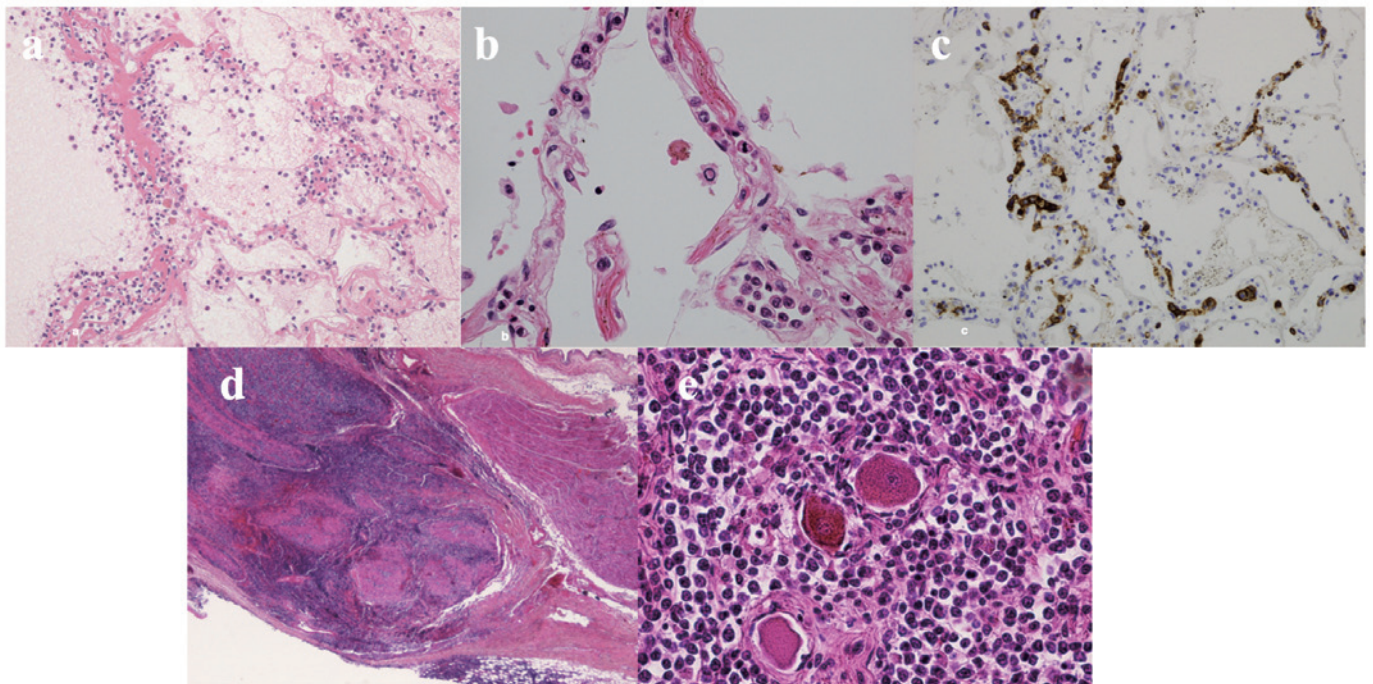
Regarding the second and third points, based on the lack of invasive lesions in the BM and skin on autopsy, it was impossible to diagnose IVLBCL using BMB and RSB in this patient. However, the autopsy findings, such as the massive invasion of other organs, including the lungs, and the increase in LDH and sIL-2R levels at the first visit suggested underlying lymphoma invasion in multiple organs without PET/CT imaging. Respiratory disturbance is one of the main manifestations of IVLBCL, with a detection rate of approximately 30% on imaging and 60% on autopsy.<sup>3-5</sup> Furthermore, a previous case study reported that the mass can be detected by PET/CT during the clinical course even



**Fig. 2.** Pathological and immunohistochemical findings of left trigeminal nerve biopsy. Histological analysis at low magnification (*a*, HE×200) and high magnification (*b*, HE×400) of the trigeminal nerve tumor. Atypical infiltrating cells are negative for the expression of CD3 (*c*), CD5 (*e*), and CD10 (*f*), and positive for the expression of CD20 (*d*), BCL6 (*g*), and IRF4/MUM-1 (*h*).



**Fig. 3.** Postmortem macroscopic findings of the trigeminal nerve tumor. Macroscopic findings of the trigeminal nerve tumor (*a*). A hemorrhagic mass was observed (yellow circle). Histological analysis at lower magnification (*b*, HE×200) and higher magnification (*c*, HE×400) of the trigeminal nerve tumor. Atypical cells infiltrated the endoneurium of the trigeminal nerve. Tri; trigeminal nerve.



**Fig. 4.** Autopsy findings of the lung and lumbar nerve root. Histological analysis of the lung at low magnification (*a*, HE×200) and high magnification (*b*, HE×400) showing intravascular atypical cell infiltration. Atypical infiltrating cells are positive for the expression of CD20 (*c*). Histological analysis at low magnification (*d*, HE×200) and high magnification (*e*, HE×400) of the lumbar nerve root showing atypical cell infiltration.

though negative results were obtained during the first investigation of patients with IVLBCL.<sup>11</sup> Although RSB and BMB are excellent diagnostic modalities to detect IVLBCL, with a positive rate of 50–83%,<sup>6,12</sup> PET/CT commonly fails to detect invasion in these areas. To diagnose such patients, the lungs can be examined through lung biopsy using bronchoscopy. Indeed, the rapid respiratory failure in this patient was a specific clinical manifestation, as lung manifestations among patients with IVLBCL typically progress within a couple of months.<sup>13,14</sup> Based on our experience, early bronchoscopy is useful in the early diagnosis of IVLBCL, even though our patient presented with no respiratory symptoms when BMB and RSB yielded no findings.

In summary, we presented the rare case of a TN tumor, as the first manifestation, in a patient who died due to the progression of respiratory failure and was diagnosed with IVLBCL following autopsy. There may be another subtype of IVLBCL that results in mass formation, particularly in the PN, such as neurolymphomatosis.

## CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest associated with this report.

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