

Intravascular large B cell lymphoma masquerading as acute disseminated encephalomyelitis

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CASE STUDY

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ABSTRACT

Intravascular large B cell lymphoma (IVLBCL) is a rare condition with a predilection for central nervous system involvement and is often misdiagnosed. This case report describes a 58-year-old gentleman who presented with paraparesis and subsequent dramatic neurological deterioration initially attributed to acute disseminated encephalomyelitis. Upon post-mortem examination, the correct diagnosis of intravascular large B cell lymphoma was reached. This condition has a poor prognosis but can be chemotherapy responsive. It is hoped that this case report will raise awareness of a rare and diagnostically challenging illness.

Key Words

Intravascular large B cell lymphoma, Central nervous system ADEM, Acute disseminated encephalomyelitis, chronic lymphocytic leukaemia

Implications for Practice:

1. What is known about this subject?

Intravascular large B cell lymphoma is a rare disorder and the true incidence is unknown. It displays a predilection for skin and central nervous system (CNS) involvement.

2. What new information is offered in this case study?

This case study serves to illustrate a neurological presentation of a life-threatening illness and the importance of early biopsy.

3. What are the implications for research, policy, or practice?

Intravascular large B cell lymphoma is a challenging mimic for medical practitioners. It requires a high index of clinical suspicion. Furthermore, early biopsy for diagnosis and treatment is recommended.

Background

Intravascular large B cell lymphoma (IVLBCL) was first described by Pflieger and Tappeiner in 1959.¹ It was initially characterised as an endothelial cell tumour, but is now known to arise from B-cells. Unlike other lymphomas, IVLBCL does not tend to cause lymphadenopathy, but instead resides in the vasculature adherent to the endothelium.² It is a notorious clinical mimic as it affects a myriad of bodily systems and can present with non-specific signs.

As a rare disorder, most data are drawn from individual case reports or small case series showing IVLBCL has a median age of onset of 70 years and an estimated incidence of one in 1,000,000.³ Patients often develop non-specific clinical features (e.g., fever, functional decline) initially⁴ and interestingly, the condition often displays a predilection for the central nervous system (CNS) and the skin.⁵

Neurologically, it can present with a bewildering array of clinical features, including transverse myelitis, meningoencephalitis, encephalopathy, and stroke-like

syndromes.⁵ Cutaneously, IVLBCL exhibits protean manifestations ranging from single to multiple lesions of variable morphology.⁴ There are reports of IVLBCL affecting other body systems causing nephrotic syndrome, haemophagocytosis, interstitial lung disease, myocardial infarction and fever of unknown origin.^{6–10}

Not surprisingly, reaching an early and accurate diagnosis can prove immensely challenging to clinicians. In fact, the disease is often not recognised at the outset, thus leading to delayed biopsy. Consequently, diagnosis is often established post-mortem in view of the attendant high mortality rate when untreated.⁴ Fortunately, the condition can respond to chemotherapy.² Accordingly, a high index of suspicion coupled with early biopsy is crucial.

Case details

We report a case of a 58-year-old ex-smoker who presented to our institution with rapid onset paraparesis and incontinence which had evolved over several hours. Six weeks earlier, he had received vaccination for influenza and tetanus. His background history was notable for haemachromatosis, type 2 diabetes mellitus, ischaemic heart disease, coronary artery bypass grafting, cerebral infarction (subtle residual left hemiparesis), osteoarthritis, and chronic lymphocytic leukaemia (quiescent, under regular haematological surveillance). Relevant medications at presentation included aspirin, a statin, an antihypertensive, and insulin. Socially, he was independent, lived with his wife, and drank minimal alcohol. There was no history to suggest exposure to illicit drugs or human immunodeficiency virus (HIV).

On initial assessment, myelopathy was suspected based on the patient's paraparesis and examination findings of brisk lower limb reflexes and extensor plantar responses. An initial urgent magnetic resonance imaging (MRI) of the spinal cord identified high signal change in the thoracic cord (Figure 1). In view of the pre-existing history of vascular disease, normal MRI and MR angiography (MRA) brain on admission (Figure 2, Panel A), and rapidity of initial presentation, spinal cord stroke was considered the most likely aetiology and he was initially managed supportively. However, over the first week, the patient's paraparesis progressed to paraplegia with urinary retention. The progression of symptoms over days and imaging findings raised the differential possibility of post-vaccination or inflammatory transverse myelitis. Consequently, he was treated with high-dose intravenous methylprednisolone. A lack of any meaningful clinical improvement prompted a trial of plasma-exchange, which was also unsuccessful.

Over the following four weeks, his clinical condition deteriorated further with mild upper limb weakness and periods of delirium and drowsiness. These symptoms appeared to respond favourably but transiently to empirical intravenous methylprednisolone with relapse days later. Investigation with electroencephalography three weeks into his admission revealed non-specific slowing and excluded non-convulsive status epilepticus. Repeat MRI of the brain at the same juncture (Figure 2, Panel B) identified new diffuse cerebral hyperintensities in keeping with a diagnosis of acute disseminated encephalomyelitis (ADEM) and thus, a five-day course of intravenous immunoglobulin was provided but this was also to no avail. Further clinical deterioration was accompanied by seizures necessitating intubation and transfer to the intensive care unit (ICU) at the end of his fourth week of admission. There, he developed worsening delirium, quadriparesis and respiratory failure. Subsequent repeat MRI of the brain and spine in the fifth week of admission confirmed the presence of diffuse CNS inflammation.

At no stage during the patient's admission was any interval radiological improvement seen. Extensive laboratory studies were negative aside from a serum white cell count of $13 \times 10^9/L$ on admission. Serum anti-neuronal antibodies were negative. No serum paraprotein was detected. Computed tomography of the chest, abdomen, and pelvis with contrast was unremarkable. Cerebrospinal fluid (CSF) analysis on admission revealed protein 2.06g/dL (high), monocytes $76 \times 10^6/L$ (high), polymorphs $5 \times 10^6/L$ (high), and red cells $12 \times 10^6/L$. Oligoclonal bands were not detected in the CSF.

Two other neurologists (one internal and one external) provided second opinions just prior to his admission to ICU, concurring that a working diagnosis of post-vaccination ADEM was most likely. Brain biopsy was raised as a potential diagnostic option however, following lengthy discussion with the patient's family in the ICU, a consensus was reached that a palliative approach was preferable. Offers to administer cyclophosphamide empirically to treat a presumed immune-mediated condition were declined as the patient had previously expressed a wish not to receive chemotherapy. Hours later and five weeks after arrival, the patient died.

After securing consent from family members, a non-coronial autopsy was requested. Unexpectedly, multiple areas of ischaemic change, infarction, and haemorrhage (old and new) were identified throughout the CNS. Further analysis using immunohistochemistry confirmed a diagnosis of

IVLBCL. The treating team subsequently met with the patient's family in the presence of a social worker to explain the findings.

Discussion

IVLBCL is a rare form of extranodal diffuse large B cell lymphoma. Despite the presence of malignant cells in the vasculature, non-invasive and peripheral blood testing is usually non-diagnostic in this disease and of particular note, peripheral blood smears/films are usually unhelpful.³ Fortunately, some laboratory study abnormalities may be seen including elevated lactate dehydrogenase and erythrocyte sedimentation rate; thrombocytopenia; and leukopenia.^{3,4} Radiologically, there is no pathognomonic pattern of IVLBCL yet MRI is usually abnormal, showing T2 and fluid attenuated inversion recovery sequence (FLAIR) hyperintensities suggesting ischaemia or demyelination with these lesions often being multiple and metachronous.¹¹ Cerebral positron emission tomography (PET) has been described to display increased uptake in IVLBCL lesions¹² and may be considered though literature on its use in IVLBCL is limited to case reports. CSF is often abnormal often demonstrating a lymphocytosis however, in most patients neither cytology nor flow cytometry of CSF specimens is diagnostic.¹³

While a non-invasive diagnostic paradigm has been described,¹² the diagnostic modality of choice is biopsy of affected tissue. Needless to say, brain biopsy is associated with potentially life-threatening complications (e.g., intracerebral haemorrhage) and is prone to sampling errors. The hallmark of IVLBCL on histopathology is the presence of large malignant lymphocytes sequestered and often filling small vessels in affected tissues. The presence of CD20+ lymphoid cells within the lumen of blood vessels is essential for the diagnosis.^{14,15} A close inspection of the skin for lesions is important as it can provide an alternative, more amenable site for diagnostic biopsy. In one case series, 15 of 38 patients with intravascular lymphoma initially presented with skin changes.⁴

Our patient's pre-existing chronic lymphocytic leukaemia (CLL) diagnosis raises the issue of IVLBCL and its association with other haematological malignancies. IVLBCL has been reported to arise in patients with pre-existing lymphomas,¹⁶ and the presence of the CD5 cell surface marker normally present in CLL cells has been described in IVLBCL cases.¹⁷ This association of IVLBCL with pre-existing haematological malignancies however is exceedingly rare, poorly characterised, and described only in case reports.

Current treatment options are guided largely by expert opinion, published case series, and extrapolation from other lymphoma treatment protocols. The rarity of IVLBCL precludes the conduct of a major clinical trial. Most authors favour an anthracycline-based regimen such as cyclophosphamide, doxorubicin, vincristine, and prednisone with the addition of rituximab.¹⁸ Autologous stem cell transplant on remission may be considered. Although most intravascular lymphoma patients experience some response to chemotherapy, the long-term prognosis remains poor with a median treated survival of 12 months.^{3,4}

Conclusion

This case report describes a neurological presentation of IVLBCL. A rare, challenging condition with protean manifestations, IVLBCL displays a predilection for neurological and cutaneous involvement. While the long-term prognosis is poor, most patients respond to chemotherapy. This highlights for medical practitioners the importance of a high index of clinical suspicion which can lead to early biopsy, diagnosis, and consideration for chemotherapy treatment.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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PATIENT CONSENT

The authors, *Lee J and Carmody J* declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient in this report.
2. All possible steps have been taken to safeguard the identity of the patient.
3. This submission is compliant with the requirements of local research ethics committees.

Figure 1: Sagittal MRI thoracic spine T2 short tau inversion recovery (STIR) sequence on admission demonstrating mid thoracic cord lesion



Figure 2: Axial MRI brain (T2 FLAIR sequence) on admission (Panel A) and at five weeks (Panel B) demonstrating the rapid development of diffuse cerebral white matter hyperintensities

