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INTRAVASCULAR LARGE B-CELL LYMPHOMA PRESENTING WITH RHABDOMYOLYSIS AND INFLAMMATORY MYOSITIS: A DIAGNOSTIC CHALLENGE

Queen Okereke[1], John Wood[2,3], Alana Gedrose[4]

[1] Department of General Medicine, Cairns Hospital, Cairns, Australia
[2] Department of Rheumatology, Cairns Hospital, Cairns, Australia
[3] College of medicine and dentistry, James Cook University, Cairns, Australia
[4] Department of Haematology, Cairns Hospital, Cairns, Australia

Corresponding author's e-mail: Queen.Okereke@health.qld.gov.au

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ABSTRACT

Introduction: Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive extranodal lymphoma characterised by the proliferation of lymphoma cells within small blood vessels. Distinctively, IVBCL typically lacks the lymphadenopathy, discrete tumour masses, or circulating lymphoma cells characteristic of other lymphomas. This results in substantial diagnostic delays and historically high rates of postmortem diagnosis. Common clinical features of IVLBCL include fever of unknown origin, cytopenias, elevated lactate dehydrogenase, and neurological dysfunction. This case highlights the diagnostic challenges of IVLBCL and an unusual presentation with rhabdomyolysis and inflammatory myositis.

Case description: An 80-year-old man presented with recurrent falls, progressive lower limb weakness, fever, and a left foot drop. Investigations revealed bicytopenia, acute kidney injury, and markedly elevated creatine kinase (peaking at 11,200 U/l). Despite extensive negative investigations including positron emission tomography scans and bone marrow biopsy, his condition deteriorated with progressive neurological impairment and evidence of myositis on magnetic resonance imaging (MRI). The diagnosis was established by random deep skin biopsies obtained from clinically normal-appearing skin.

Conclusion: IVLBCL should be considered in patients with unexplained fever, cytopenias, and neurological decline. Rhabdomyolysis and myositis-like MRI findings are rare but important manifestations. Random incisional skin biopsy is a key diagnostic tool, offering a high diagnostic yield even in the absence of cutaneous lesions. Early recognition of this clinical constellation and timely random skin biopsy can facilitate diagnosis and enable potentially life-prolonging therapy.

KEYWORDS

Intravascular large B cell Lymphoma, random skin biopsies, myositis

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LEARNING POINTS

- Intravascular large B-cell lymphoma (IVLBCL) should be suspected in older patients presenting with unexplained fever, cytopenias, elevated lactate dehydrogenase, and progressive neurological dysfunction, particularly when conventional imaging and bone marrow biopsies are unrevealing.
- IVLBCL may masquerade as an inflammatory myositis, representing an under-recognised manifestation of the disease.
- Random deep skin biopsy even from clinically normal-appearing skin is a valuable diagnostic tool in suspected IVLBCL, with reported diagnostic yields of above 75%; and should be performed early in the diagnostic workup.

INTRODUCTION

Intravascular large B-cell lymphoma (IVLBCL) is a rare and aggressive extranodal lymphoma characterized by the proliferation of malignant B cells within small- and medium-sized blood vessels[1]. Unlike conventional lymphomas, IVLBCL does not form discrete masses or cause significant lymphadenopathy. Instead, the malignant cells proliferate within vascular lumina, leading to vessel occlusion and downstream tissue ischemia. This distinctive pathophysiology, compounded by a cytokine-driven systemic inflammatory response, produces a broad and non-specific presentation, most commonly including fever of unknown origin, constitutional symptoms, neurological dysfunction, and cutaneous involvement[2].

IVLBCL is classified into three variants: classical, cutaneous, and hemophagocytic syndrome-associated variant. The classical variant features systemic symptoms, cytopenias, elevated lactate dehydrogenase (LDH), and frequent neurological or multiorgan involvement. Neurological manifestations are variable and may include encephalopathy, stroke-like episodes, myelopathy, radiculopathy, peripheral neuropathy, and progressive motor deficits. Hemophagocytic syndrome-associated variant presents with features of hemophagocytic lymphohistiocytosis (HLH), including fever, cytopenias, hepatosplenomegaly, and bone marrow involvement, and carries a particularly poor prognosis. The cutaneous variant, accounting for approximately 25% of cases, typically presents with skin lesions without systemic involvement, carries a more favourable prognosis, and has a predilection for younger females[3]. IVBCL occurs most commonly in older people (median age 70 years) and has no sex predilection.

CASE DESCRIPTION

An 80-year-old man with a history of type 2 diabetes, hypertension, peripheral vascular disease, and previous cervical laminectomy presented with a three-week history of recurrent falls and progressive lower limb weakness. On admission, he was febrile (38.9°C), hypotensive (92/58 mmHg), and tachycardic (112 bpm). Neurological examination revealed a left foot drop with sensory loss in the left L5–S1 dermatomal distribution. No lymphadenopathy, hepatosplenomegaly, skin lesions, or muscle tenderness were identified. The remainder of systemic examination was unremarkable

Initial investigations demonstrated bicytopenia (haemoglobin 83 g/l, platelets 89 $\times 10^9$/l), acute kidney injury (creatinine 211 µmol/l), and mixed-pattern liver dysfunction. Markedly elevated creatine kinase (peaking at 11,200 U/l), elevated LDH (1,240 U/l), and a C-reactive protein of 88 mg/l were also noted. Computed tomography scan of the chest, abdomen, and pelvis showed mild splenomegaly without lymphadenopathy or an identifiable infective source. Despite empirical broad-spectrum antibiotics and supportive therapy for rhabdomyolysis, the patient remained persistently febrile. Repeated blood cultures, urine cultures, respiratory viral panels, autoimmune serologies, and serum protein electrophoresis were all unremarkable. soluble interleukin-2 receptor (sIL-2R) levels was elevated at 7857pg/ml (cut off < 2678pg).

Over the following five weeks, his condition progressively deteriorated. He developed bilateral moderate proximal lower limb weakness and urinary retention. Worsening renal and hepatic dysfunction, persistent fevers, and progressive bicytopenia requiring regular red cell transfusions were also observed. Magnetic resonance imaging (MRI) of

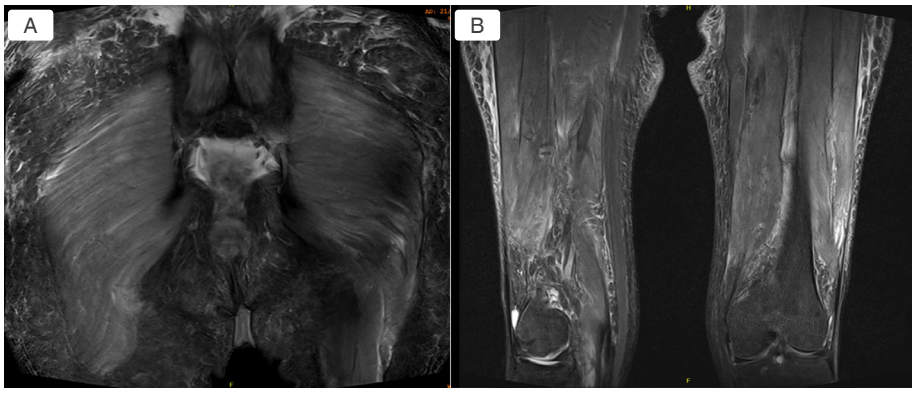


Figure 1. Magnetic resonance imaging. A) T2 weighted images of the gluteus maximus and B) bilateral thigh muscles show extensive oedema representing myositis.

the lower limbs *(Fig. 1)* demonstrated extensive oedema involving the gluteal and thigh musculature, suggestive of myositis, although no muscle tenderness was ever elicited in this patient. MRI of the brain and whole spine, electromyography, echocardiography, and serial septic screens were non-diagnostic. Two positron emission tomography (PET) scans failed to identify a neoplastic, inflammatory, or infectious focus; however, progressive splenomegaly (20 cm) and bilateral pleural effusions subsequently developed. Bone marrow examination showed no evidence of lymphoma, hemophagocytic lymphohistiocytosis, or significant dysplasia.

Despite extensive negative investigations, the constellation of persistent fever, progressive neurological impairment, cytopenias, splenomegaly, and markedly elevated LDH raised strong suspicion for occult lymphoma, particularly intravascular large B-cell lymphoma (IVLBCL). Random incisional skin biopsies were therefore obtained from clinically uninvolved skin of the abdomen and thighs approximately two months into the admission. Flow cytometry of the specimens revealed clonal B cell population. Histopathological examination *(Fig. 2)* revealed atypical intravascular lymphoid cells within the deep dermis and subcutaneous tissue, with immunohistochemistry demonstrating diffuse expression of CD19, CD20, PAX5, and BCL2, confirming the diagnosis of IVLBCL.

The patient declined chemotherapy and received high-dose corticosteroids. This resulted in resolution of fevers, reduced transfusion requirements, and partial recovery of renal and hepatic function; however, his neurological deficits remained unchanged. He was subsequently discharged with palliative care and died one month later.

DISCUSSION

Our patient exhibited several features of the classical IVLBCL variant including persistent fever, progressive neurological dysfunction, cytopenias, splenomegaly, and markedly elevated LDH. Neurological manifestations occur in over half of IVLBCL patients. The patient's foot drop, progressive lower limb weakness, sensory loss, and urinary retention are consistent with the microvascular occlusive nature of the disease. The elevated soluble interleukin-2 receptor (sIL-2R) levels raised concern for secondary HLH; however, the patient did not meet diagnostic criteria for the hemophagocytic syndrome-associated variant[4].

An unusual aspect of this case was the marked creatine kinase elevation (peaking at 11,200 U/l) and MRI findings suggestive of myositis. IVLBCL has been reported to masquerade as inflammatory myopathy with muscle oedema, weakness, and elevated muscle enzymes, although this presentation is uncommon[5]. This finding is due to the disease involvement of the small vessels of the muscles causing muscle injury and inflammation. The detection of the positive anti-OJ autoantibody, a rare myositis- specific antibody suggested the presence of antisynthetase syndrome. However, the overall clinical picture did not fit this diagnosis. Furthermore, the absence of muscle tenderness despite extensive MRI abnormalities

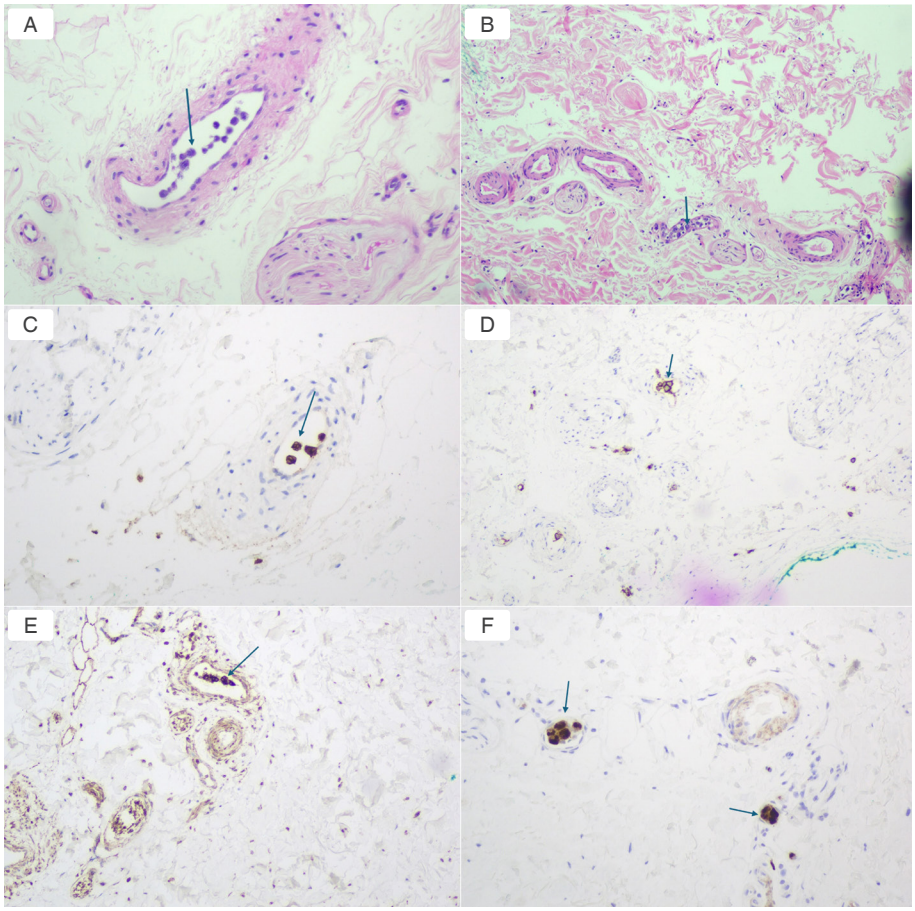


Figure 2. *A, B) Histopathological examination of the deep dermis demonstrated large atypical lymphoid cells confined to the lumina of small blood vessels. Hematoxylin and eosin stain; C) Immunohistochemical staining revealed diffuse positivity for CD 19; D) CD 20; E) BCL2; F) PAX5 confirming the diagnosis of intravascular large B- cell lymphoma.*

may represent an important clue distinguishing IVLBCL-related muscle involvement from primary inflammatory myositis.

The diagnosis of IVLBCL remains notoriously challenging, as standard investigations, including cross-sectional imaging, PET, peripheral blood examination, and bone marrow biopsy are often unrevealing despite advanced disease[6], as seen in this patient. The absence of lymphadenopathy and fluorodeoxyglucose-avid disease was particularly misleading in this case; however, the persistence of classical lymphoma-associated features raised a high index of suspicion for an occult haematological malignancy.

Random incisional skin biopsy is a valuable diagnostic tool for IVLBCL. Diagnostic yield is maximized by sampling the deep dermis and subcutaneous fat, preferentially from visible skin lesions when present, with ≥3 biopsies from different anatomical sites (e.g. arm, thigh, and abdomen). Importantly, high diagnostic yield is reported even in normal appearing skin in IVLBCL cases[7,8]. In our patient, random incisional biopsies from normal-appearing skin of the abdomen and thighs established the diagnosis after two months of extensive but unrevealing investigations.

The patient's transient clinical improvement following corticosteroid therapy with resolution of fevers and improvement in cytopenias and organ dysfunction further supports the diagnosis. Corticosteroids may provide temporary symptomatic relief but are not curative. IVLBCL remains an aggressive lymphoma with a poor prognosis when untreated as seen in this patient. Rituximab-containing anthracycline-based chemoimmunotherapy remains the standard of care and has significantly improved survival outcomes compared with historical series[9,10].

This case highlights the importance of considering IVLBCL in patients with unexplained fever, cytopenias, elevated LDH, neurological deterioration, or multiorgan dysfunction, particularly when standard investigations remain unrevealing. Early recognition of this characteristic clinical constellation and timely random deep skin biopsy may facilitate diagnosis and enable potentially life-prolonging therapy.

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