Case Report

Case report of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements presenting as compartment syndrome of the leg

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Background: Diffuse large B-cell lymphoma (DLBCL)/high-grade B-cell lymphoma with MYC and BCL2 rearrangements ("double-hit" lymphoma) is an uncommon subtype of mature B-cell lymphoma characterized by the concurrent rearrangements of MYC and BCL2 oncogenes. Rarely, aggressive high-grade lymphomas manifest as compartment syndrome, necessitating urgent surgical intervention. Here, we describe a case of high-grade B-cell lymphoma with an unusual presentation of compartment syndrome.

Case Description: A 68-year-old woman presented to the emergency room with increased swelling and pain in her right leg, was subsequently diagnosed with right thigh compartment syndrome, and underwent urgent fasciotomy followed by repeat debridement in the medical wound closure. Additionally, the patient was found to have inguinal and external iliac lymphadenopathy along with deep vein thrombosis (DVT). Her past medical history included human immunodeficiency virus (HIV) infection, which was well-controlled with bictegravir, emtricitabine, and tenofovir alafenamide. Excisional biopsy of the right thigh muscle and fluorescence in situ hybridization (FISH) analysis confirmed the diagnosis of high-grade B-cell lymphoma with *MYC* and *BCL2* gene rearrangements arising in the setting of immunodeficiency/dysregulation (lymphoma associated with HIV infection). Despite aggressive medical management in the intensive care unit, the patient succumbed to the disease and ultimately died from sepsis and hemorrhagic shock.

Conclusions: High-grade B-cell lymphoma with MYC and BCL2 rearrangements represents an aggressive lymphoma with a poor prognosis. The unusual manifestation of this lymphoma involving skeletal muscle and presenting as compartment syndrome is rare. Unfortunately, the patient passed away shortly after undergoing debridement surgery. This case highlights the importance for clinicians to be vigilant and attentive to atypical presentations, as delays in diagnosis and treatment can have significant consequences. Early recognition and prompt intervention are crucial in saving the patient's life.

Keywords: Case report; compartment syndrome; diffuse large B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements; "double-hit" lymphoma

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Introduction

Background

High-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements is an aggressive mature B-cell lymphoma characterized by concurrent *MYC* and *BCL2* gene rearrangements (1). It is known for its aggressive clinical course and poor outcomes, with 4- to 5-year overall survival rates of approximately 40–50% (2). Timely oncological management is crucial for patients' care. Clinical symptoms can vary depending on the site of involvement, but commonly manifest as lymphadenopathy with "B symptoms". Acute compartment syndrome is a medical emergency characterized by painful swelling around muscles and the accumulation of excess pressure within the fascia surrounding the muscle, often associated with injury or repetitive stress. This condition can be life-threatening as it leads to tissue necrosis and permanent damage (3). Diagnosis typically relies on clinical presentation, medical history, imaging studies, and measurement of intercompartment pressure (ICP). Surgical intervention is necessary to treat acute compartment syndrome (4).

Rationale and knowledge gap

Acute compartment syndrome can be associated with exceedingly rare but treatable conditions, such as aggressive B-cell lymphoma/high-grade B-cell lymphoma with *MYC* and *BCL2* gene arrangements. However, early recognition and diagnosis of this uncommon etiology of compartment syndrome can be very challenging, yet crucial for the timely management of patients.

Objective

In this case report, we describe a case of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements infiltrating the muscle and initially presenting as compartment syndrome. We also performed a literature review of all reported cases of lymphoma present as compartment syndrome and discuss the diagnostic challenges for this unique presentation of lymphomas. This manuscript is written following the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-24-154/rc).

Highlight box

Key findings

- We reported a case of aggressive B-cell lymphoma/high grade B-cell lymphoma with *MYC* and *BCL2* gene arrangements presenting as compartment syndrome, which resulted in a poor clinical outcome.

What is known and what is new?

- Acute compartment syndrome is life-threatening and can be associated with aggressive lymphoma.
- "Double-hit" lymphoma presented as compartment syndrome is exceedingly rare, and this is the first case report of its kind.

What is the implication, and what should change now?

- This case highlights the diagnostic challenges, emphasizing the importance of early recognition of uncommon etiologies including high grade B cell lymphoma of compartment syndrome.
- The timely management is crucial for the optimal clinical outcome.

Case presentation

A 68-year-old woman was brought to the emergency room with complaints of increased swelling and pain in her right leg, accompanied by weight loss and loss of appetite over the past 2 to 3 weeks. The patient's medical history includes human immunodeficiency virus (HIV) infection treated with bictegravir, emtricitabine & tenofovir alafenamide, untreated hepatitis C, and a history of right breast cancer treated with lumpectomy and radiation therapy. Notably, there was no history of hematological malignancy. Physical examination revealed tenderness to palpation in the right leg with swelling extending from below the right inguinal ligament to the toes, along with pitting edema and palpable pulses. Non-compressible right femoral and popliteal veins were noted and suggestive of right lower extremity deep vein thrombosis (DVT). Angiography did not provide solid evidence of DVT; however, vasculature details were obscured by the soft tissue mass and associated necrosis. Given the presence of pulmonary embolism and clinical suspicion of DVT, a heparin drip was initiated for anticoagulation management, and an inferior vena cava (IVC) filter was placed. The patient's HIV infection was well-controlled, with an undetectable viral load and a CD4 count of 828 cells/cmm (normal range, 332–1,642 cells/cmm) and a CD4/CD8 ratio of 3.63 (normal range, 0.7–4.8).

The abdominal computed tomography (CT) scan revealed severe asymmetric enlargement of the right leg compared to the left, accompanied by the loss of fat planes, decreased attenuation of the musculature, and diffuse

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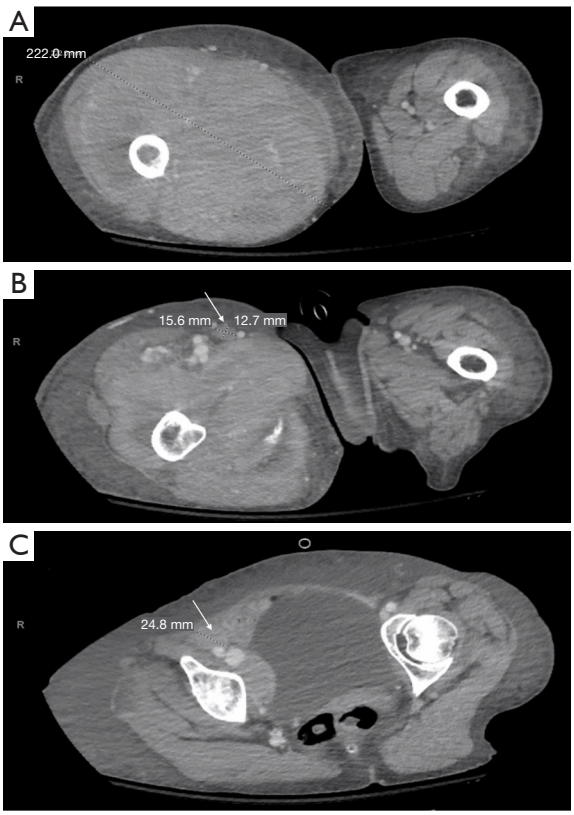

Figure 1 Abdominal CT images show severe soft tissue swelling in the right thigh and enlarged lymph nodes. (A) Images from abdominal CT found severe asymmetrical enlargement of the right leg compared to the left with diffuse subcutaneous edema. On abdominal CT, the presence of an enlarged right inguinal lymph node (B) and right external iliac lymph node (C) were noted, as indicated by arrows in the images. "R" indicates the right side. Dashed lines indicate the sizes of measurements. CT, computed tomography.

subcutaneous edema (*Figure 1A*). A subsequent magnetic resonance imaging (MRI) of the right lower extremity confirmed the presence of severe swelling and edema within the thigh musculature, suggestive of myonecrosis and/or intramuscular abscesses. Enlarged lymph nodes were also noted on the abdominal CT, with the right inguinal lymph node measuring up to 1.6 cm and the right external iliac lymph node measuring 3.4 cm × 2.5 cm × 2.2 cm (*Figure 1B,1C*). Furthermore, a pulmonary embolism was identified on the CT angiography (CTA) of the chest.

The clinical history, radiological studies, and laboratory findings were evaluated and revealed concerns for compartment syndrome and rhabdomyolysis. Subsequently, the patient was diagnosed with compartment syndrome in the right thigh based on elevated compartment pressure measurements. The suspected underlying causes included bacterial infections leading to myositis, myonecrosis, osteomyelitis, or abscesses. Multiple blood cultures returned negative results. Broad-spectrum antibiotics were initiated, followed by an urgent fasciotomy and two subsequent debridement surgeries.

The soft tissue specimen was obtained from right thigh debridement excision and revealed dense confluent lymphoid infiltrates extending into the skeletal muscles. The infiltrate primarily consisted of monotonous, moderate-sized lymphocytes with round nuclei, dispersed chromatin, and indistinct nucleoli (*Figure 2*). Both small and large lymphocytes were noted, accompanied by tingible body macrophages and apoptotic bodies. Brisk mitotic activity was observed. No abscesses or acute infection was detected.

Immunohistochemical analysis (*Figure 2*) demonstrated that the neoplastic lymphocytes were of B-cell lineage, as evidenced by positive staining for CD20, with a germinal center immunophenotype strongly positive for CD10. Additionally, BCL2 and MYC were strongly positive, while chromogenic *in situ* hybridization for Epstein-Barr virus-encoded RNA (EBER), cyclin D1 and SOX11 were negative. Ki-67 staining revealed a high proliferation rate ranging from 40% to 70%. Notably, no follicular dendritic cell (FDC) meshworks were identified. A minor infiltrate of mixed CD4 and CD8 positive T-cells was also observed.

Next-generation sequencing (NGS) studies demonstrated variants of *BCL2*, *DDX3X*, *EZH2*, *GNA13*, *KMT2D*, *SOCS1*, *TNFRSF14*, and *AFHX4*. Fluorescence in situ hybridization (FISH) analysis identified *MYC* and *BCL2* gene rearrangements. Given the patient's history of HIV infection, the final diagnosis of diffuse large B-cell lymphoma (DLBCL)/high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements arising in the context of immunodeficiency/dysregulation (lymphoma associated with HIV infection) was established.

Even though the patient tolerated fasciotomy and two subsequent debridement surgeries, the patient's condition continued to decline postoperatively. The patient was under supportive treatments due to do not resuscitate/do not intubate status. She experienced shock and unfortunately expired 14 days after the initial presentation due to multisystem organ failure, septic shock, and hemorrhagic shock.

All procedures performed in this study were in accordance with the ethical standards of the institutional

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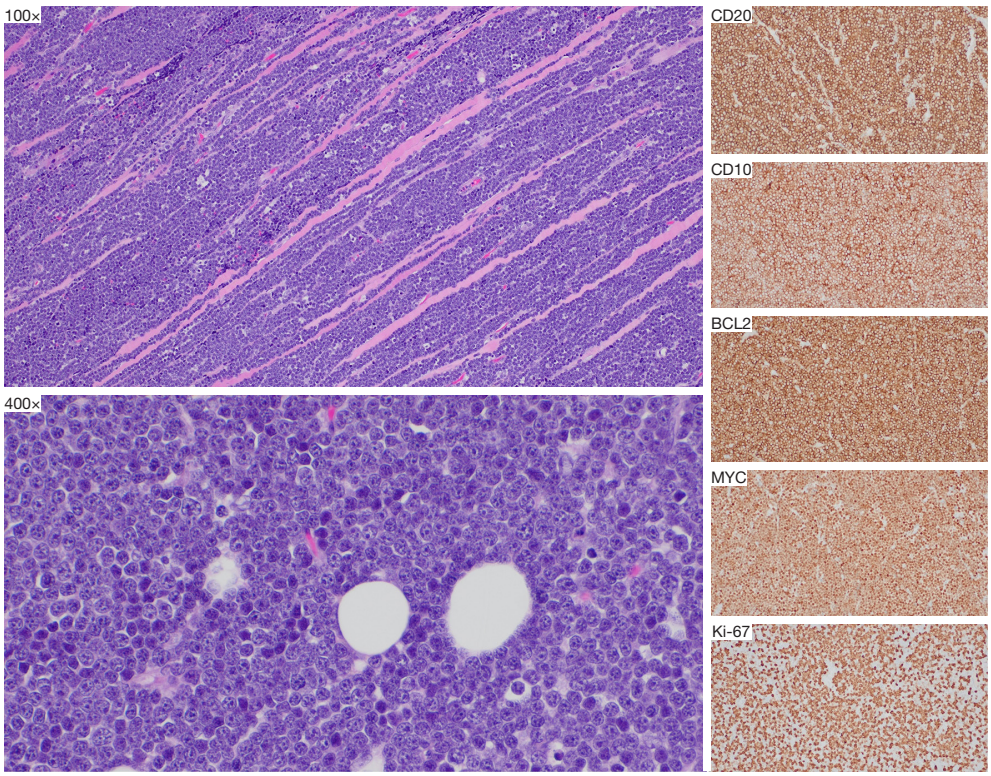

Figure 2 H&E sections of the excisional biopsy of right thigh soft tissue at 100× and 400×, and immunohistochemical stainings of paraffin-embedded tissue sections with appropriate controls of the lymphoma cells at 200× show diffuse strong positivity of CD20, CD10, BCL2, and MYC, and a high labeling of Ki-67. H&E, hematoxylin and eosin.

and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Publication of this case report and accompanying images was waived from patient consent according to the Institutional Review Board at Albany Medical College (Albany, NY, USA).

Discussion

Key findings

Here, we report a case of double-hit lymphoma initially presenting as compartment syndrome, which resulted in a poor clinical outcome.

Strengths and limitations

Only a few cases have been reported of lymphoma initially presenting as compartment syndrome with skeletal muscle infiltration. To the best of our knowledge, this is the first case report of double-hit lymphoma with an initial presentation as compartment syndrome. Due to the aggressive nature of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements and the rapid clinical course in this case, we were unable to collect information about the outcome of chemotherapy in this scenario.

Comparison with similar research

We conducted a literature review to identify all articles about lymphoma presenting as compartment syndrome, and summarized the findings in *Table 1*.

Explanations of findings

Across the literature, a variety of lymphomas, including Burkitt lymphoma (BL), DLBCL, and anaplastic large cell lymphoma (ALCL) have been reported to present as compartment syndrome (5-16). The majority of these cases reported a poor prognosis, with patients succumbing shortly after hospital admission. However, both cases of Burkitt lymphoma showed positive treatment response

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Table 1 Summary of cases reported for lymphoma presented as compartment syndrome

Authors	Age (years)	Gender	Anatomic location	Histologic diagnosis	Treatment	Follow-up
Munoz E, *et al.* (5)	64	Male	Right forearm	Relapsed double hit high grade B cell lymphoma	n/a	n/a
Hendrick JM, *et al.* (6)	18	Male	Cecum, peritoneal	Burkitt lymphoma	Oncological treatment	Patient became better at 18 days
Egyed E, *et al.* (7)	42	Male	Small intestine	Burkitt lymphoma	R-CHOP	Patient discharged after 2 months
Syed F, *et al.* (8)	61	Male	Left lower leg	DLBCL	R-CHOP	Patient achieved good clinical response
Stewart CM, *et al.* (9)	79	Male	Bilateral orbital	Richter transformation	Dexamethasone, radiotherapy	Died at 1 week
Lal H, *et al.* (10)	35	Female	Right upper leg	NHL B cell type	Supportive treatments	Died during hospitalization
Bozkurt MA, *et al.* (11)	80	n/a	Retroperitoneum	NHL	Supportive treatments	Died at day 10
Southworth SR, *et al.* (12)	80	Female	Left leg	NHL	n/a	n/a
Takahashi Y, *et al.* (13)	73	Male	Left upper eyelid	NK/T cell lymphoma	CHOP	Died at 2 months
Chim CS, *et al.* (14)	34	Male	Left sacrospinalis	ALCL	M-BACOD	Disease free for 4 years
Terpe F, *et al.* (15)	11	Male	Abdomen	B-ALL/LBL	Daunorubicin and clinical trial	Died at day 6
Li JY, *et al.* (16)	62	Female	Left lower leg	B-ALL/LBL	Supportive treatments	Died at day 22

DLBCL, diffuse large B-cell lymphoma; NHL, non-Hodgkin lymphoma; NK, natural killer; ALCL, anaplastic large cell lymphoma; B-ALL/LBL, B-acute lymphoblastic leukemia/lymphoblastic lymphoma; R-CHOP, cyclophosphamide, doxorubicin, prednisone, rituximab and vincristine regimen; CHOP, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone regimen; M-BACOD, methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone regimen; n/a, not available.

and excellent prognosis (6,7). This highlights a crucial clinical consideration: aggressive lymphoma should always be considered when patients present with compartment syndrome, warranting timely hematological and oncological treatment.

Implications and actions needed

In our case, despite the patient undergoing multiple surgeries for debridement, the patient succumbed to her condition a few weeks after admission. The pathological diagnosis was made 14 days after the patient's initial encounter, with the molecular report being generated 6 days after the patient's demise. Such delay raises concern about rapid initial clinical diagnosis, prolonged turnover time and shortages of staff, especially in the post-pandemic era, which have been reported to impact medical system (17,18). Efficient communication and collaboration among clinicians, pathologists, and all medical staff are essential to ensure the delivery of high-quality medical care to all patients.

Conclusions

In summary, we presented a rare case of high-grade B-cell lymphoma with *MYC* and *BCL2* rearrangements initially presenting as compartment syndrome. Hematological malignancies manifesting in uncommon sites with atypical syndromes pose significant challenges for diagnosis, particularly in clinical emergencies. It is important to be cautious when encountering unusual presentations of compartment syndrome, as they may be associated with underlying systemic diseases, including high-grade aggressive lymphomas. Early recognition and prompt

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diagnostic evaluation are essential for ensuring timely and appropriate management and optimizing patient outcomes.

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Footnote

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