



Case Report

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Unilateral Lower Extremity Swelling as an Unusual Presentation of Non-Hodgkin's B-Cell Lymphoma



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Citation Sahraiyani S, Abbaszadeh M, Aminishakib P, Rahmani Tanha R, Karimpour Reyhan S. Unilateral Lower Extremity Swelling as an Unusual Presentation of Non-Hodgkin's B-Cell Lymphoma. Case Reports in Clinical Practice. 2021; 6(1):15-19.

Running Title Unusual Presentation of Non-Hodgkin's B-Cell Lymphoma

ABSTRACT

Non-Hodgkin's B-cell lymphoma is a hematological condition with different types based on clinical presentation, pathological features, and therapeutic response, like Diffuse Large B-cell Lymphoma (DLBCL), follicular lymphoma, and Chronic Lymphocytic Leukemia (CLL). We report A 33-year-old male presented with a complaint of unilateral leg swelling, firstly supposed to be a Deep Vein Thrombosis (DVT); however, in multiple Doppler ultrasonography, DVT was ruled out. The patient's precise history revealed a swollen mass in the left knee region for two months that slowly enlarged and was confirmed with a physical examination. Doppler ultrasonography of the lower extremities conducted in our center presented no sign of deep vein thrombosis; however, it demonstrated some complex conglomerate lymph nodes in the left inguinal compressing the ipsilateral femoral and iliac vein. It also revealed bulky adenopathy, with a 95×65 mm left knee mass. The performed biopsy reported the existence of malignant lymphoma, suggesting the existence of DLBCL. Consequently, he was referred to a hematology/oncology department for appropriate treatment. This unusual presentation of DLBCL and the importance of noticing an accurate history taking and physical examination, instead of conducting unnecessary paraclinical tests (several Doppler ultrasonography in this case), have led us to report this case.

Article info:

Received: 30 Dec 2020

Revised: 12 Jan 2021

Accepted: 09 Feb 2021

Keywords:

Edema; Lymphoma; Swelling; Diffuse large B-cell lymphoma; Lymphadenopathy; Venous thrombosis

Introduction

Lower extremities edema is a condition with increased interstitial fluid in the lower limb. This leg swelling can be unilateral or bilateral ede-

ma. One of the most frequent causes of unilateral lower extremities swelling is related to the venous system. Venous insufficiency can be due to venous thrombosis, post-thrombotic states, venous valvular insufficiency, or external pressure, which impair venous drainage. There

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exist other differential diagnoses of unilateral lower extremities edema; leg swelling in a paralyzed limb, lymphangitis or lymph obstruction, Baker's cyst, cellulitis, and knee abnormality or idiopathic. It is a symptom and not a diagnosis; thus, the challenge is to correctly diagnose and manage the initial cause [1, 2]. Diagnostic approach on lower extremities edema depends on the time of onset, unilateral or bilateral, positional or non-positional, pitting or non-pitting, etc [3]. Besides, the treatment is based on the initial causes.

Turning to Diffuse Large B-cell Lymphoma (DLBCL), it typically presents with an enlarging symptomatic mass, mostly in the neck, abdomen, or mediastinum. Systemic "B" symptoms (fever, weight loss, night sweats) are observed in approximately 30% of patients [4].

Case Presentation

A 33-year-old male was admitted to Imam Khomeini Hospital with a two-month history of progressive swelling of the left lower limb. At the admission time, he provided a Doppler ultrasonography report of the lower extremities without signs of deep vein thrombosis. In a more precise history taking, the patient noted a swollen mass in his left knee region for about two months that slowly enlarged to the size of a peanut, then bigger. He also experienced the enlargement of the left inguinal region and progressive swelling as well as pain in the left lower limb.

The patient mentioned nausea and the loss of appetite; however, he denied any constitutional symptoms, such as fever, chills, night sweats, fatigue, or recent weight loss. His medical history included Hepatitis B (HBV) infection and interferon therapy 5 years ago. He denied other medical or surgical histories. Physical examination revealed an oriented and cooperative young man. The patient was hemodynamically stable, afebrile, and normotensive. His head and neck examination result were unremarkable. Cardiopulmonary, abdominal, and neurological examinations were unremarkable.

Left lower extremity examinations revealed pronounced firm swelling of the left limb. His left leg was two times larger in circumference than his right leg with pitting edema and a negative Homan's sign (Figure 1). A 7×6 cm firm, fixed, and nodular mass with irregular borders was

palpable in the left groin. Additionally, a 5×3 cm firm, fixed, and nodular mass with irregular borders was palpable in the left knee. No lymph nodes were palpable in the neck, axilla, and right groin. Femoral, popliteal,

and dorsalis pedis pulses were not palpable, because of gross edema. Electrocardiography (ECG) was normal and a conventional X-ray illustrated no pathologic findings.

Laboratory evaluation was remarkable for mild anemia, as follows: RBC=3.52×10¹²/L; HGB=9.5 g/L; MCV=79; HCT=27.8. His white blood cell count was equal to 6.8×10⁹/L and platelets 375×10⁹/L. He presented a positive HBS Ag result, but Anti-HCV and HIV-Ab were negative. Other laboratory test results were as follows: serum iron=30; ferritin=227; TIBC=246; ESR=62; CRP=37; Alb=3.3; total pro=6.2; folic acid=6.2; vit B12=139.9; AST=28 U/L; ALT=25 U/L; ALP=349 U/L; Bil.T=0.4; Bil. D=0.2; PT=11.5; INR=1.0; APTT=25; Na=133 mmol/L; K=3.6 mmol/L; BS=96; urea=48; uric acid=9; Mg=2.5 mmol/L; phosphorus=3.0 mmol/L. On admission, the patient had Ca=12.7 and Cr=3.3 which decreased to Ca=10.2 and Cr=1.8 by appropriate treatment.

Subsequently, a Doppler ultrasonography of the lower extremities was performed; no sign of deep vein thrombosis was detected, but it revealed an irregular shaped, hypoechoic, mixed cystic solid mass measuring 98×67 mm. This mass seemed to be complex conglomerate lymph nodes in the left inguinal compressing the ipsilateral femoral and iliac vein. It also revealed bulky adenopathy, with a 95×65 mm left knee mass. Furthermore, the pelvic magnetic resonance imaging demonstrated an 83×60 mm lobulated left para-iliac and an 82×53 mm left inguinal mass lesions in favor of lymphadenopathy, enhancing adjacent left iliac and left femoral vessels (Figure 2). No abnormalities were noted in the chest or abdomen Magnetic Resonance Imaging (MRI).

Consequently, a guided core needle biopsy of knee mass was conducted for the histological definition of the suspected lymphoproliferative disease. The biopsy data revealed the existence of malignant lymphoma, Diffused B-cell Non-Hodgkin's Lymphoma (Figure 3). An immuno-



Figure 1. Severe swelling of the left lower limb

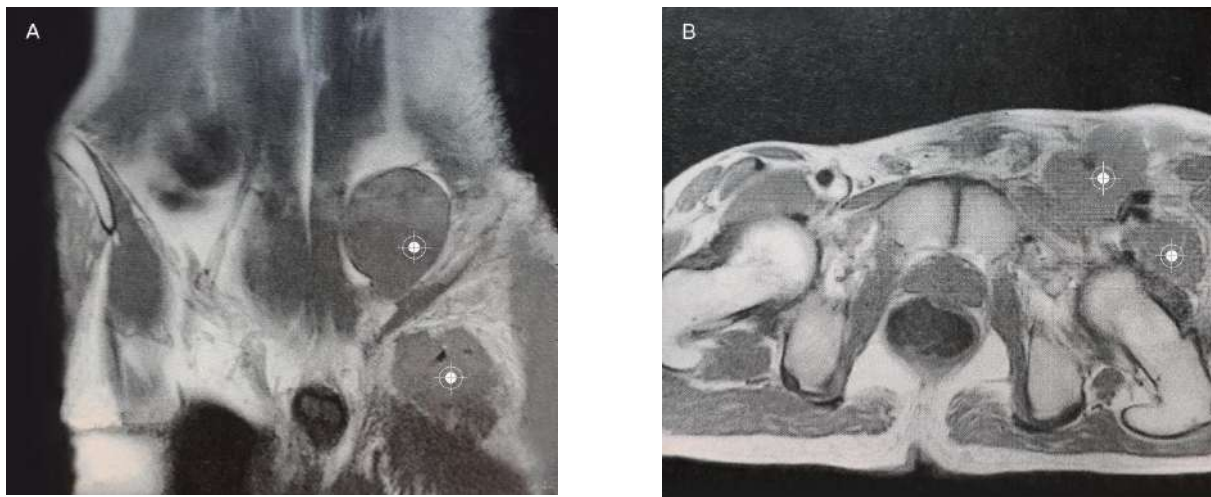


Figure 2. T1-weighted MRI of the pelvis without contrast

A. Coronal view; and B. Axial view, showing left para-iliac and inguinal mass lesions.



histochemical study was carried out; accordingly, tumor cells were positive for Vimentin and CD20. There were scattered CD3⁺ in the background. No CD99, CD30, or CD10 were detected in the tumor. Proliferative activity (Ki67) was 65%-70% (Figure 4).

Discussion

Due to chronic unilateral lower extremity edema and other findings in the history and physical examination, our top differential diagnoses included lymphoma, cellulitis, venous insufficiency, thrombophlebitis, Deep Vein Thrombosis (DVT), and soft tissue or bone neoplasms.

Initially, we requested a Complete Blood Count (CBC) for assessing comorbidities, viral markers, including HBS Ag, anti-HCV, and HIV-Ab due to the patient's history and risk factors, ESR and CRP for inflammatory factors, ECG and Chest X-ray (CXR) for ruling out heart failure, kidney function tests, Doppler ultrasonography of the lower extremities to rule out DVT and assess left knee mass; we found those in the physical examination. Concerning viral markers, HBS Ag was positive and HIV-Ab and Anti-HCV were negative; the patient also reported these in his medical history. In CBC, he presented low hemoglobin levels with MCV=79. Creatinine levels were high. ECG and CXR were normal. ESR and CRP were high. Doppler ultrasonography of the lower extremities revealed no sign of DVT; however, it reported mixed cys-

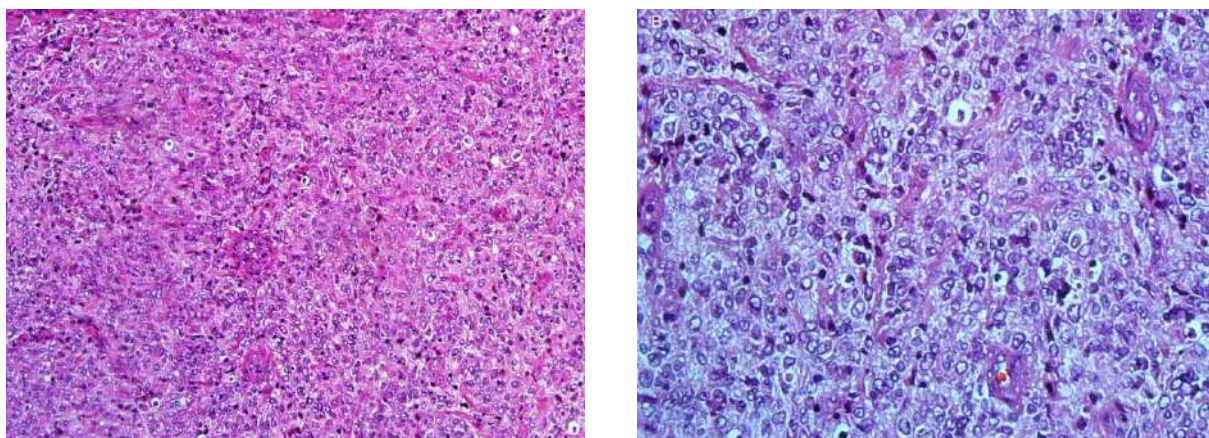


Figure 3. The histopathologic studies of biopsy specimens, indicating infiltration with a population of large B cells consistent with malignant lymphoma

A. Low-power magnification; Hematoxylin and Eosin (H&E) staining $\times 20$ magnification: The normal architecture of the lymph node was completely effaced by the lymphoma; B. At high-power magnification H&E staining $\times 40$ magnification of the infiltrated area; the neoplastic lymphocytes were large, with a large, round, and irregular nucleus and coarse chromatin with multiple nucleoli and scant cytoplasm.



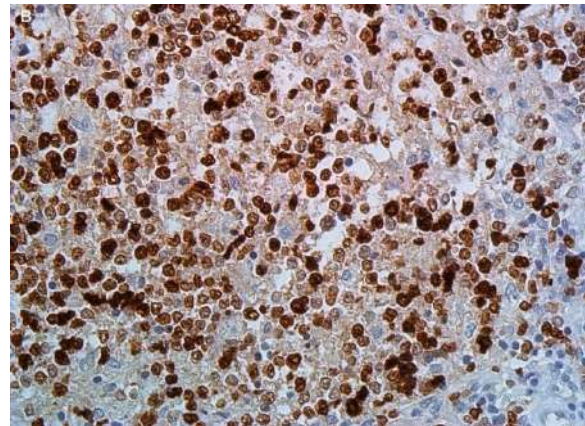
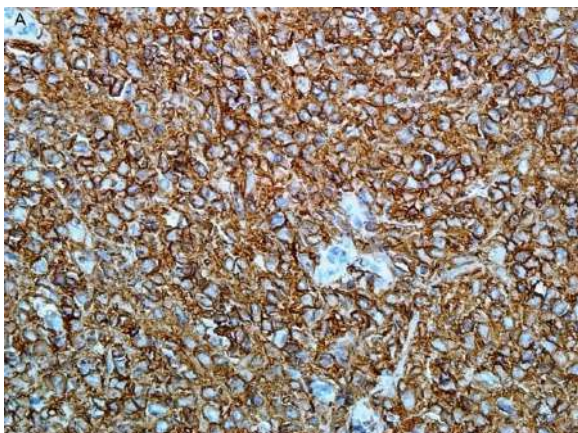


Figure 4. Immunohistochemical staining

A. The lymphoma cells expressed B cell marker (CD20); B. The proliferation index by Ki67 was estimated at 65-70 %. (×40 magnification).



tic solid in the left inguinal. Such complications seemed to be complex lymph nodes compressing the ipsilateral femoral and iliac veins. The relevant examination results also reported bulky adenopathy in the left knee.

Thus, in the second step, we requested an iron profile due to the patient's low Hgb and low MCV, i.e. compatible with chronic inflammatory diseases anemia. We also requested pelvic MRI which reported an 83×60 mm lobulated left para-iliac and an 82×53 mm left inguinal mass lesions in favor of lymphadenopathy, enhancing adjacent left iliac and left femoral vessels. Accordingly, it was concluded that the mechanical obstruction of the blood vessels in the groin determined the lower limb lymphedema. Our diagnosis was limited to lymphoma, lymphadenopathy due to unknown origin neoplasm, granulomatous diseases, or infectious causes.

In the third step, we requested a core needle biopsy of an enlarged inguinal lymph node and knee mass, i.e. compatible with malignant lymphoma. Therefore, in the fourth step, we requested an immunohistochemically study to determine the type of lymphoma. It was positive for CD3, CD20, and vimentin, i.e. compatible with DLBCL. The patient was diagnosed with non-Hodgkin lymphoma of B-cell type. Consequently, he was referred to a hematology/oncology department.

Lymphomas are hematological conditions in which lymphocyte or white blood cells in lymphoid tissue manifest malignant features in pathological results. The main lymphoma types are Hodgkin's Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL). These types affect different cells and have various treatment interventions and clinical presentations. Non-Hodgkin lymphoma is more common and responsible for 90% of the cases [5]. Non-Hodgkin's B-Cell Lymphoma has different types based on clinical presentations, pathological fea-

tures, and treatment, like DLBCL, follicular lymphoma, and Chronic Lymphocytic Leukemia (CLL). Its' incidence peak ranges at the age of 40 to 60 years. Its prevalence is increasing which makes it a more important part of the cancer burden worldwide [6, 7]. It has different causes and predisposing factors, including infectious agents, such as HCV, HIV, and EBV. Chemical agents, genetic susceptibility, and autoimmune diseases may be associated with NHL. In the clinical presentation, symptoms such as painless lymph nodes enlargement, night sweating, weight loss, chest or abdominal pain, and fever are more common; however, it can be presented by any symptom-based on tumor localization and how far malignancy is disseminated and involve other organs beside lymphoid tissues [8]. Unilateral lower extremity lymphedema is considered possible; however, it has a rare initial presentation for Non-Hodgkin's lymphoma [9]. DLBCL is the most common type of NHL; it has an aggressive and fatal clinical course and presents extranodal disease symptoms [10]. It is associated with HCV infection. The diagnosis is based on the history data and tissue biopsy, especially excisional biopsy [11]. The relevant treatment includes 6 to 8 cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or a short course of chemotherapy, followed by involved-field radiotherapy [12, 13]. Other combinations and approaches may also be used for treatment [14].

Conclusion

The reported case highlighted the variety in the presentation of lymphoma as well as the importance of precise history taking, physical examination, and following a step-by-step approach to unilateral lower extremity edema. Although unilateral lower extremity edema is rare as the ini-

tial presentation of lymphoma, clinicians must be aware of lymphoma as a possible cause of this presentation.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgements

The authors would like to appreciate the support and constructive comments of the methodologist research development office, Imam Khomeini Hospital Complex, Tehran.

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