CASE REPORT

Unilateral lower extremity swelling as a rare presentation of non-Hodgkin's lymphoma

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SUMMARY

Lower extremity oedema is frequently encountered in clinical practice. The challenge is to correctly identify the aetiology of oedema, and hence correctly manage the cause. Oedema can be classified as venous oedema and lymphoedema. Lymphoedema of the lower extremities is usually bilateral. Unilateral leg lymphoedema may occur secondary to radiation, surgery, compression by a tumour or early filariasis infection. Unilateral lower extremity lymphoedema has been reported as a rare initial presentation for lymphoma, mostly in women, usually without B-symptoms, and often with inguinal lymphadenopathies or abdominal masses. In this paper, we report a rare case of unilateral lower extremity oedema in a healthy male presenting to the outpatient clinic following trauma; further work-up revealed non-Hodgkin's lymphoma with bulky inguinal lymphadenopathy compressing the iliac veins.

BACKGROUND

Lower extremity oedema is a frequent symptom in the primary care setting. The most common cause is venous insufficiency, which usually manifests bilaterally.¹ Other common differential diagnoses are secondary lymphoedema, lipoedema and complications from ipsilateral limb surgery.² It is the presentation of unilateral leg oedema that often poses a diagnostic challenge to physicians in the ambulatory setting. Further complicating this issue is the paucity of case reports and diagnostic guidelines in the literature related to unilateral leg oedema.

Unilateral lower extremity oedema can be classified into acute or chronic duration. The acute onset of unilateral leg oedema can point to a diagnosis of thrombophlebitis, especially with the presence of inflammation such as increased warmth, tenderness and erythema. A more insidious development or chronic duration of unilateral leg oedema can be easily misdiagnosed as venous insufficiency. In actuality, such a presentation may be an atypical manifestation of an occult malignancy causing lymphatic or venous obstruction.³ Bilateral lower extremity oedema is a common manifestation of lymphoma; yet here we present a rare case report of a healthy male patient with unilateral lower extremity oedema secondary to lymphoma.

CASE PRESENTATION

A 60-year-old generally healthy Asian man presented to the primary care clinic for his annual visit. He reported excellent health until about 2 weeks ago when he sustained trauma to his left

leg after twisting his left ankle and falling directly onto his left lower leg. He developed a large haematoma at the site of injury, which gradually resolved by the time of visit. However, he had persistent left calf pain, redness and swelling. Compression stockings and leg elevation had not helped to improve his symptoms. He was concerned, as these leg symptoms had been progressing over the course of 2 weeks. He denied any weakness, paresthesia, pallor or coldness to the left leg. He further denied any fevers, night sweats, weight loss, dyspnoea, exercise intolerance, orthopnea or postural nocturnal dyspnoea. He reported no recent travel, prolonged immobilisation or bed rest. His medical history consisted only of hyperlipidaemia and hypertension with no surgical histories and no history of malignancy or tobacco use. On physical examination, his vital signs were stable including a body mass index (BMI) of 23. Cardiopulmonary examination showed clear lungs, 2+ equal dorsalis pedis pulses and no jugular venous distention (JVD). Abdominal and neurological examinations were unremarkable. Left lower extremity examinations revealed severe swelling with +2 pitting oedema, mild erythema, increased warmth and moderate tenderness of the left leg—all extending from the mid-thigh to the ankle. A new enlarged 2 cm×1.5 cm, tender left inguinal lymph node was noted. No other lymphadenopathies were palpable. The right lower extremity was normal on examination. As part of the outpatient evaluation of this unilateral leg oedema, a STAT X-ray of the left tibia, fibula and ankle showed no fractures. A STAT lower extremity venous Doppler ultrasound was negative for deep venous thrombosis (DVT). At this point, the left lower extremity oedema and inguinal adenopathy were felt to be secondary to the recent trauma with a resultant thrombophlebitis. He was instructed to use cold compresses and over the counter ibuprofen as needed for the pain control. A close follow-up appointment was scheduled for 2–3 weeks.

INVESTIGATIONS

Two weeks later, the patient presented to an outside emergency department with a significantly worsening left leg swelling. A CT scan of the abdomen and pelvis showed left aortic lymphadenopathy and bulky lymphadenopathies alongside the left iliac vessels, extending to the left inguinal region with compression of the left iliac vein (figures 1 and 2). Given concerns of lymphoma, the patient underwent a left inguinal lymph node biopsy, which revealed diffuse large B-cell

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Figure 1 A CT scan of the abdomen and pelvis in the axial view. The arrow points to the enlarged left iliac lymph nodes.

lymphoma. A subsequent bone marrow biopsy showed no evidence of lymphoma. A positron emission tomography (PET) scan demonstrated the malignancy as mainly infradiaphragmatic with primary involvement of the left supraclavicular and posterior mediastinal lymphadenopathy.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses in this case involve local and systemic causes of unilateral lower extremity swelling associated with erythema and tenderness. Local aetiologies include cellulitis, thrombophlebitis, DVT, acute trauma, Baker's cyst and venous insufficiency. Systemic aetiologies may include hypoalbuminaemia, congestive heart failure, compression by a tumour and protein-losing nephropathy or gastropathy.

TREATMENT

The patient subsequently received six cycles of R-cyclophosphamide, hydroxydaunorubicin (also called doxorubicin or adriamycin), oncovin (also called vincristine),

Figure 2 A CT scan of the abdomen and pelvis in the coronal view. The arrow points to the enlarged left iliac lymph nodes.

prednisone (CHOP) therapy (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone).

OUTCOME AND FOLLOW-UP

With chemotherapy, his unilateral leg oedema improved significantly, although it did not completely resolve. He is now undergoing lymphatic massage therapy as an adjunct treatment for his secondary lymphoedema. A repeat PET scan after completion of chemotherapy showed no evidence of residual disease.

DISCUSSION

Unilateral lower extremity oedema is commonly encountered in the outpatient setting. It can be classified into acute onset (oedema starting <72 h) or chronic duration (oedema persisting >72 h). Acute unilateral lower extremity oedema is usually due to DVT or trauma. Chronic unilateral lower extremity oedema is commonly due to venous insufficiency and less commonly due to lymphoedema, either primary or secondary.¹ Secondary lymphoedema develops as a result of disruption or obstruction of the lymphatic system by surgery, tumour or infection, for example, filariasis.^{1–4} In developed countries, the most common cause of secondary lymphoedema is malignancy. On the other hand, filariasis is considered the most common cause of secondary lymphoedema in developing countries.^{2–4}

The history and physical examination play a vital role in the diagnostic evaluation of unilateral lower extremity oedema. Key questions in the history should include the duration of the oedema, the painfulness of the oedema and any improvement of the oedema overnight with leg elevation, a complete list of medications and any history of systemic disease including sleep apnoea and malignancy or radiation in the abdominal/pelvic region. Key components of the physical examination should include the BMI value, distribution of the oedema, tenderness of the oedema site, presence of pitting oedema and varicose veins, any skin changes and any signs of systemic disease including abdominal/pelvic masses or lymphadenopathies.¹ With these key details of the history and physical examinations at hand, the clinician must then make an important decision on the urgency of the evaluation needed—whether the work-up can be postponed to a future visit (eg, an asymptomatic individual with stable chronic leg oedema) or must be expedited at the current appointment (eg, an individual with acute onset of oedema at <72 h or an unstable individual with symptoms of acute dyspnoea or signs of DVT). In our patient, we excluded the possibility of a DVT with a Doppler ultrasound. His lower extremity examination showed no signs of venous insufficiency. He had no other alarming features or risk factors on the history and examination including no B-symptoms and no history of abdominal/pelvic diseases or travel outside the USA to point us initially to secondary lymphoedema. The temporal onset of his symptoms with trauma accompanied by signs of inflammation on the leg examination led us to the diagnosis of acute left leg thrombophlebitis with reactive inguinal adenopathy. A close outpatient follow-up was subsequently planned.

A review of the literature, however, reveals that unilateral lower extremity oedema may be the initial and sometimes the only manifestation in patients with secondary lymphoedema from occult malignancy. Hawkins *et al*³ found that of 10 cases of secondary lymphoedema from lymphoma, unilateral leg oedema was the only presenting symptom in seven cases, with a duration as long as 6 months before diagnosis. Inguinal lymphadenopathy or lower abdominal mass was noted in all the cases. Similarly, another report of 35 cases of secondary lymphoedema from neoplasms noted palpable inguinal lymph nodes in all

eight lymphoma cases with three cases having oedema as the first manifestation of the disease.⁵ In three of the cases reported by Hawkins *et al*,³ the patients were misdiagnosed as venous insufficiency but failed to respond to conventional modalities such as leg elevation, diuretics, anti-inflammatory agents and compression stockings. This led the authors to assert that the response of unilateral leg oedema to therapy may serve as an important impetus for a renewed diagnostic investigation and reassessment of the treatment results.

Non-Hodgkin's lymphoma typically presents with painless progressive lymphadenopathy and commonly with bilateral leg oedema.⁶ Unilateral lower extremity lymphoedema is considered a possible but rare initial presentation for non-Hodgkin's lymphoma.^{1 3 7 8}

This presentation is more common in women^{3 7} and there are usually no associated B-symptoms (eg, weight loss, anorexia and night sweats), making for low clinical suspicion in our male patient. A close examination for inguinal lymphadenopathy or

abdominal masses may provide a key clue for the diagnosis of lymphoma.³ A CT scan is the standard procedure for the assessment of disease extension.⁶ Excisional biopsy with histological examination of the lymph nodes is the gold standard for the diagnosis of the non-Hodgkin's lymphoma subtype.⁹ A pretreatment PET scan is recommended before initiation of chemotherapy; however, PET scans are more widely used to assess the response to therapy.¹⁰

In conclusion, this case highlights the clinical importance of incorporating a classification scheme for unilateral lower extremity oedema into acute and chronic duration, based on certain details in the history and physical examination. The presence of inguinal lymphadenopathies, the failed response to conventional oedema therapy and the lack of B-symptoms seen in the case are key clinical cues in the diagnosis and management of unilateral leg oedema secondary to lymphoma.

Competing interests None.

Patient consent Obtained.

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Learning points

- ▶ Clinicians must maintain a high clinical awareness of lymphoma as a possible aetiology of unilateral lower extremity oedema.
- ▶ Classifying unilateral lower extremity oedema into acute and chronic duration is important in its diagnostic work-up.
- ▶ Despite its rare occurrence, unilateral leg oedema can be the initial and sometimes the only finding in those with occult lymphoma. Often, there are no B-symptoms and no response to the conventional oedema therapy.
- ▶ The presence of inguinal lymphadenopathy or abdominal masses should raise the index of suspicion.
- ▶ The early recognition of these clinical clues may expedite the diagnosis and treatment of an otherwise occult and rapidly progressive malignancy.

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